RANDOMISED CONTROLLED STUDY COMPARING ORAL METOPROLOL AND ORAL PREGABALIN FOR ATTENUATION OF CARDIOVASCULAR RESPONSES TO LARYNGOSCOPY AND TRACHEAL INTUBATION

Dissertation submitted

in the partial fulfillment of the requirements

for award of the degree

M.D (Anaesthesiology)

Branch X

GOVT .KILPAUK MEDICAL COLLEGE

CHENNAI - 10

THE TAMIL NADU DR.M.G.R MEDICAL UNIVERSITY,

CHENNAI, TAMIL NADU

APRIL 2016

CERTIFICATE

This is to certify that this dissertation entitled "**RANDOMISED CONTROLLED STUDY COMPARING ORAL METOPROLOL AND ORAL PREGABALIN FOR ATTENUATION OF CARDIOVASCULAR RESPONSES TO LARYNGOSCOPY AND TRACHEAL INTUBATION"** submitted by **Dr. NANDHINI K** in partial fulfillment for the award of the degree Doctor of Medicine in Anaesthesiology by The Tamilnadu Dr.M.G.R. Medical University, Chennai is a bonafide work done by her at GOVERNMENT KILPAUK MEDICAL COLLEGE, CHENNAI during the academic year 2013-2016.

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CERTIFICATE BY THE GUIDE

This is to certify that this dissertation entitled "**RANDOMISED CONTROLLED STUDY COMPARING ORAL METOPROLOL AND ORAL PREGABALIN FOR ATTENUATION OF CARDIOVASCULAR RESPONSES TO LARYNGOSCOPY AND TRACHEAL INTUBATION"** submitted by **Dr. NANDHINI K** in partial fulfillment for the award of the degree Doctor of Medicine in Anaesthesiology by The Tamilnadu Dr.M.G.R. Medical University, Chennai is a bonafide work done by her at GOVERNMENT KILPAUK MEDICAL COLLEGE, CHENNAI during the academic year 2013-2016 under my guidance and supervision.

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DECLARATION

I, **Dr.K.NANDHINI**, solemnly declare that this dissertation, entitled "**RANDOMISED CONTROLLED STUDY COMPARING ORAL METOPROLOL AND ORAL PREGABALIN FOR ATTENUATION OF CARDIOVASCULAR RESPONSES TO LARYNGOSCOPY AND TRACHEAL INTUBATION"**, has been prepared by me, under the expert guidance and supervision of Prof. Dr.T.Murugan, M.D.,D.A Professor and HOD, Department of Anaesthesiology, Government Kilpauk Medical College and Hospital, Chennai and submitted in partial fulfillment of the regulations for the award of the degree M.D.(Anaesthesiology) by The Tamil Nadu Dr. M.G.R. Medical University and the examination to be held in April 2016.

This study was conducted at Government Kilpauk Medical College Hospital, Chennai. I have not submitted this dissertation previously to any university for the award of any degree or diploma.

Place: Chennai (DR.K.NANDHINI)
Date:

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I am extremely grateful and indebted to Prof. Dr. Valli Sathyamoorthy, M.D., D.A., Professor, Department of Anaesthesiology, Government Kilpauk Medical College, Chennai for her concern, inspiration, meticulous guidance, expert advice and constant encouragement in preparing this dissertation.

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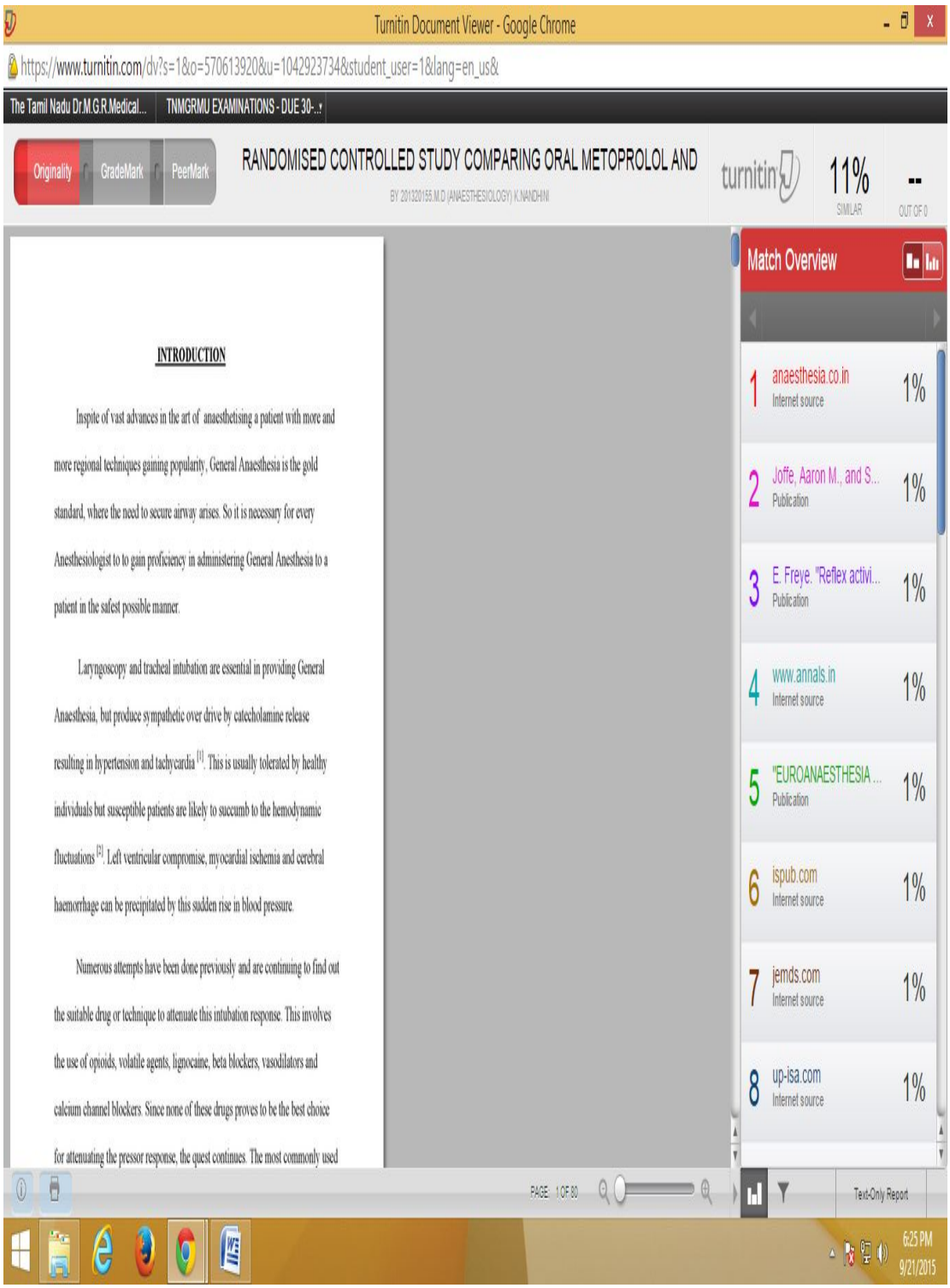
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INTRODUCTION
Inspite of vast advances in the art of anaesthetising a patient with more and more regional techniques gaining popularity, General Anaesthesia is the gold standard, where the need to secure airway arises. So it is necessary for every Anesthesiologist to to gain proficiency in administering General Anesthesia to a patient in the safest possible manner.
Laryngoscopy and tracheal intubation are essential in providing General Anaesthesia, but produce sympathetic over drive by catecholamine release resulting in hypertension and tachycardia [1]. This is usually tolerated by healthy individuals but susceptible patients are likely to succumb to the hemodynamic fluctuations [2]. Left ventricular compromise, myocardial ischemia and cerebral haemorrhage can be precipitated by this sudden rise in blood pressure.
Numerous attempts have been done previously and are continuing to find out the suitable drug or technique to attenuate this intubation response. This involves the use of opioids, volatile agents, lignocaine, beta blockers, vasodilators and calcium channel blockers. Since none of these drugs proves to be the best choice for attenuating the pressor response, the quest continues. The most commonly used
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INTRODUCTION

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ABSTRACT:

BACKGROUND:

Airway instrumentation of direct laryngoscopy and intubation are powerful noxious events that should be attenuated by appropriate premedication, smooth induction and rapid intubation. The present study evaluated the efficacies of single preoperative dose of metoprolol and pregabalin for attenuation of hemodynamic response to laryngoscopy and endotracheal intubation.

METHODS:

A total of 90 adult patients aged 18 to 45 years with American society of Anaesthesiologist physical status I and II of both the gender were randomized to receive metoprolol (100mg) group A, or group B pregabalin (150mg) or group C placebo one hour prior to surgery. HR, SBP, DBP and MAP were measured preoperatively, before induction, at the time of intubation, 1, 3, 5 and 10 minutes after intubation.

RESULTS:

Metoprolol and pregabalin proved to be effective in blunting the hemodynamic stress response to laryngoscopy and intubation when compared with the control group. In pregabalin group, there is slight increase in heart rate and

arterial pressure but are not statistically significant. There is no incidence of bradycardia or hypotension intraoperatively in any group. There is a occurrence of post operative sedation in pregabalin group, but it doesn’t interfere with the recovery of the patient.

CONCLUSION:

Oral administration of metoprolol or pregabalin was effective in suppressing the cardiovascular response to laryngoscopy and intubation. Metoprolol was superior to pregabalin because suppression of tachycardic response was less with pregabalin.

KEYWORDS:

laryngoscopy, endotracheal intubation, hemodynamic response, metoprolol, pregabalin

INTRODUCTION

Inspite of vast advances in the art of anaesthetisinga patientwith more and more regional techniques gaining popularity, general anaesthesia is the gold standard,where the need to secure airway arises. So it is necessary for every Anesthesiologist to gain proficiency in administering general anesthesia to a patient in the safest possible manner.

Laryngoscopy and tracheal intubation are essential in providing general anaesthesia,but produce sympathetic over drive by catecholamine release resulting in hypertension and tachycardia [1]. This is usually tolerated by healthy individuals but susceptible patients are likely to succumb to the hemodynamic fluctuations[2]. Left ventricular compromise, myocardial ischemia and cerebral haemorrhage can be precipitated by this sudden rise in blood pressure.

Numerous attempts have been done previously and are continuing to find out the suitable drug or technique to attenuate this intubation response. This involves the use of opioids, volatile agents, lignocaine, beta blockers, vasodilators and calcium channel blockers. Since none of these drugs proves to be the best choice for attenuating the pressor response, the quest continues. The most commonly used drugs are benzodiazepines and opioids. The effects like variability in patients

response, respiratory complications and post operative nausea and vomiting, delay in recovery of bowel function with benzodiazepines and opioids respectively, along with the stress response to surgery creates the need to find a much more suitable drug with limited side effects.

Recently, an increasing emphasis has been made on the use of non opioid drugs as a part of multimodal regimen for decreasing anxiety and the intubation response. Many recent studies show that drugs such as gabapentin and pregabalin are known to decrease stress response due to laryngoscopy and intubation.

Pregabalin is a drug with analgesic, anticonvulsant and anti anxiety effects mainly used for the management of neuropathic pain, neuralgia occurring postherpes infection and as adjuvant for the treatment of partial onset seizures. Its effectiveness in providing postoperative pain relief and reducing the dose of parenteral analgesics were well documented in several studies[3,4,5]. Only minimal evidences are available in our literature related to the cardiovascular properties of pregabalin in patients undergoing surgery. [6,7]

Hence in this study we decided to find out the efficacy of metoprolol and pregabalin in attenuating the pressor response to tracheal intubation.

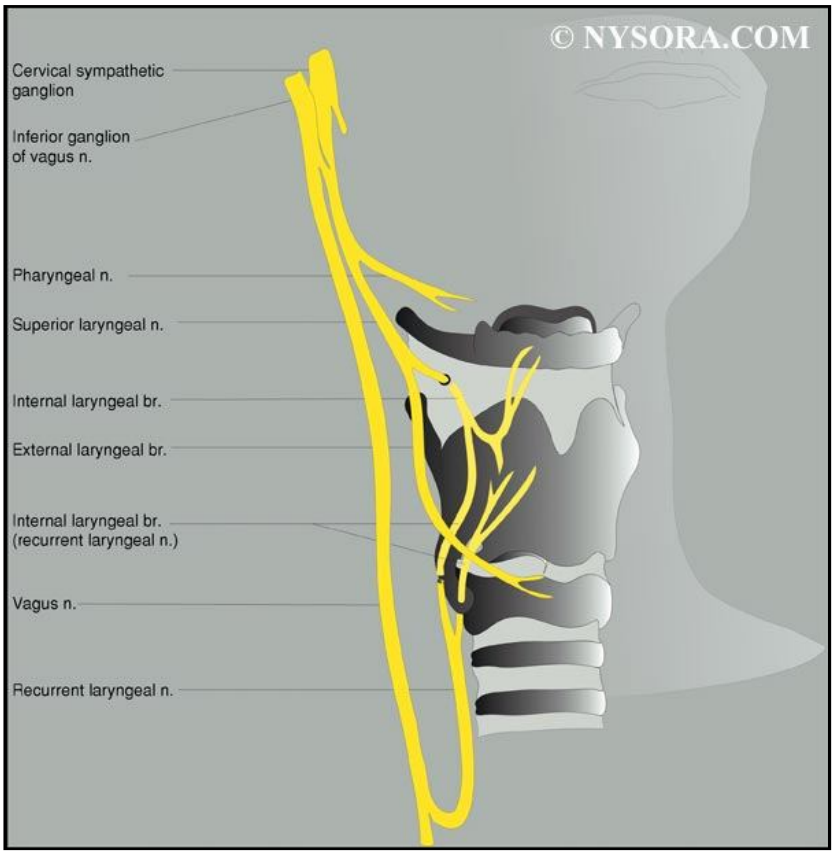
Physiology of laryngoscopy and intubation

Airway manipulations (like laryngoscopy, intubation or laryngeal mask airway insertion) are such a notorious stimulus producing more changes in cardiovascular system via reflex responses[2,8]. The duration of these responses are short lived and produce only mild or no consequences in healthy, but deleterious in patients with long standing hypertension, coronary vascular disease, hyper reactive airways and intracranial compromise.

Irritation of the airway stimulates the proprioceptors around the glottis and the trachea. These consist of small diameter myelinated fibers with mechanoreceptors, large diameter myelinated fibers with stretch receptors and polynodal endings of non myelinated nerve fibers.

The afferent impulse travels via glossopharyngeal and vagus nerve to the brain stem producing autonomic nervous system stimulation, causing tachycardia and hypertension[9]. Reid and Brace were first to describe the hemodynamic response to laryngoscopy and intubation in 1940. This is due to stimulation of cardioaccelerator nerves and sympathetic chain ganglia causing norepinephrine release from adrenergic nerves and epinephrine secretion from the adrenal medulla. In some cases there is the activation of renin - angiotensin system, with

renin release from the juxtaglomerular apparatus, which are supplied by beta adrenergic nerve terminals.



Simply to tell about sensory innervations[10,11], the posterior third of the tongue, oropharynx and anterior epiglottis are innervated by glossopharyngeal nerve. The posterior part of epiglottis and distal airways are innervated by vagus nerve.

Effects on the respiratory system:

Any acute bronchospasm or endobronchial intubation causes ventilation - perfusion mismatch leading to decrease in systemic arterial oxygen tension. And also, there is a reduction in cardiac output due to

impaired venous return to the left heart from pulmonary circulation. This is due to the occurrence of positive end expiratory pressure as one of the response to intubation. The consequences of these changes are more pronounced in patients having compromise in ventricular function or any depletion in intravascular volume.

Effects on the cardiovascular system:

The sympathetic response to manipulation of the airway leads to many complications in patients having disease in the cardiac system. The commonly seen such complication is myocardial ischemia in patients with coronary artery disease. Myocardial oxygen demand is mainly determined by inotropy of the heart and blood pressure. The increase in both these parameters during intubation leads to increased oxygen demand. This demand – mismatch gets rectified when there is an increased flow of blood in the coronary circulation. But in case of fixed coronary blood flow, this mismatch persists, leading to myocardial tissue ischemia which may progress to myocardial infarction or severe cardiac dysfunction. The end diastolic pressure of the left ventricle may also increase in addition to the already increased blood pressure thereby causing more insult by compromising the subendocardial tissue perfusion. This can be seen as a ST segment depression in the

electrocardiograph. There is also a rise in pulmonary artery diastolic pressure seen in the presence of preexisting arteriosclerosis.

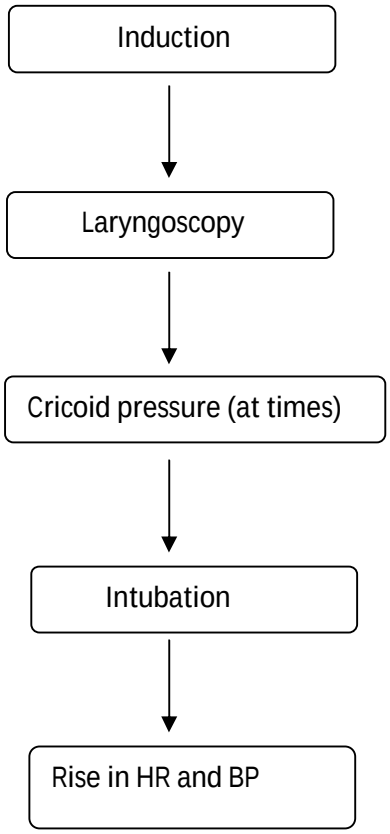
Patients with abnormalities in the vascular systemthat affects the integrity in the arterial lining are at increased risk during laryngoscopy and intubation. Any abrupt rise in blood pressure leads to rupture in the lining of the affected vessels and sudden deterioration in patient's clinical status. This is of particular importance in patients with aneurysms and arteriovenous malformations.

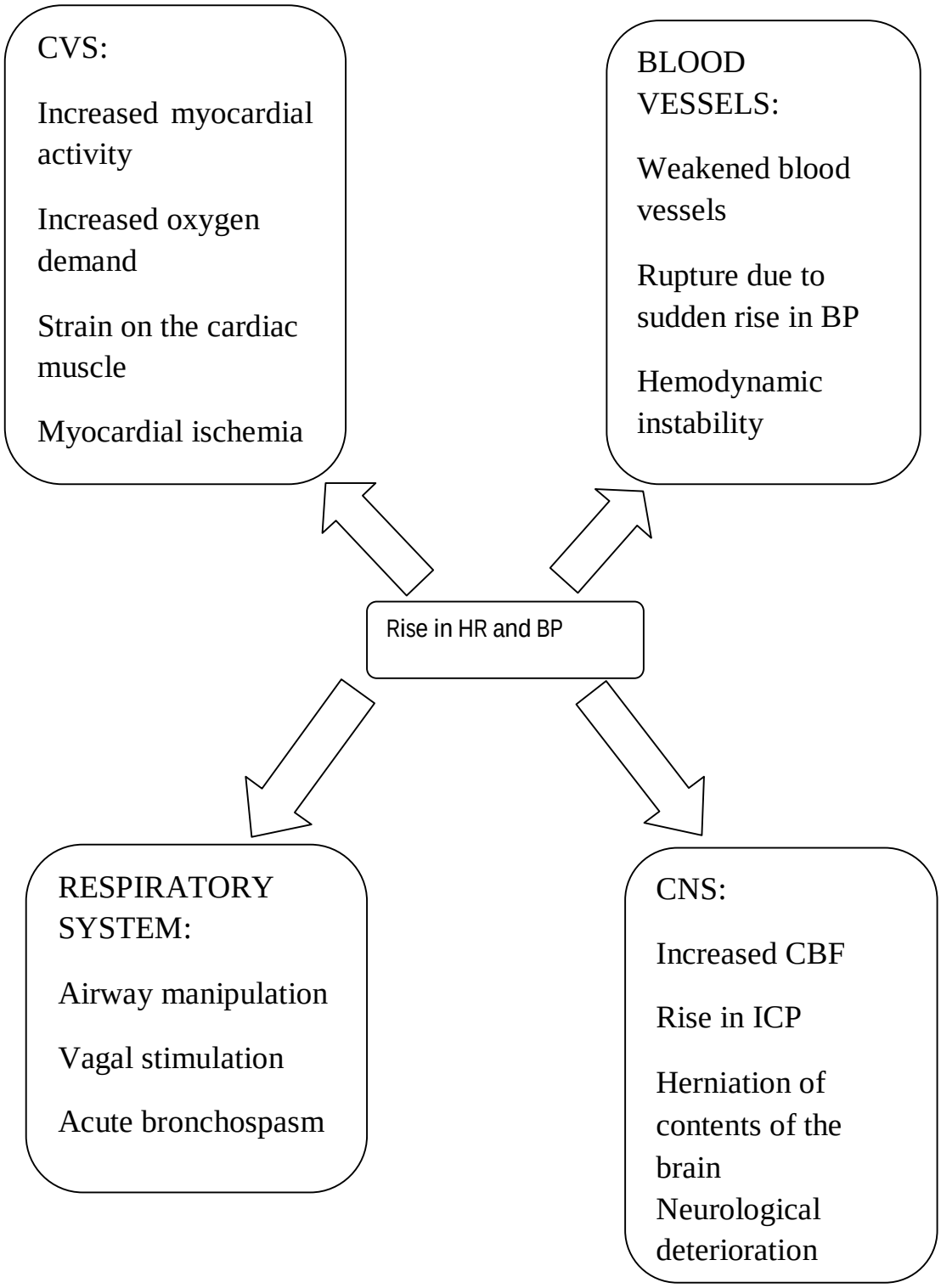
Effects on the central nervous system:

Increase in electroencephalographic activity suggests stimulation of central nervous system along with increase in cerebral metabolic rate and cerebral blood flow. This increase in blood flow causes rise in intracranial pressure leading to protrusion of brain contents and neurological deterioration in patients with reduced intracranial compliance.

Reflex response to intubation is hazardous in patients with neuropathological processes like cerebral edema, intracranial mass lesions and acute hydrocephalus. As the cerebral auto regulation is impaired in such patients,pressor response to intubation causes marked increase in cerebral blood flow and in turn intracranial pressure. Vigorous and uncontrolled coughing causes rise in pressure inside the thorax and

abdomen, which gets transmitted as rise in cerebrospinal pressure leading to impairment in perfusion of the brain. Thus, neurosurgical anesthesiologists pay meticulous attention in blunting the stress response to laryngoscopy and tracheal intubation.




CVS:
Increased myocardial activity
Increased oxygen demand
Strain on the cardiac muscle
Myocardial ischemia
BLOOD VESSELS:
Weakened blood vessels
Rupture due to sudden rise in BP
Hemodynamic instability
Rise in HR and BP
RESPIRATORY SYSTEM:
Airway manipulation
Vagal stimulation
Acute bronchospasm
CNS:
Increased CBF
Rise in ICP
Herniation of contents of the brain
Neurological deterioration

METHODS TO BLUNT THE CIRCULATORY RESPONSE TO LARYNGOSCOPY AND INTUBATION

Several techniques and various drugs have been researched in an attempt to suppress this pressor response that occurs during and after laryngoscopy and intubation.

1. Minimizing the duration of direct laryngoscopy

Limiting the duration to within 15 seconds helps in decreasing the sympathetic surge as the duration of laryngoscopy is directly proportional to the amount of sympathoadrenal discharge.

2. Minimizing the stimulation of airway proprioceptors

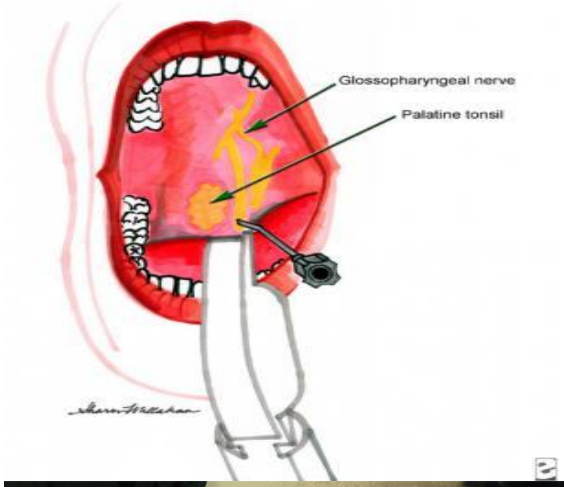
Use of curved blade for laryngoscopy (Macintosh or McCoy) instead of a straight blade (Miller) results in reduced stimulation of this sensory receptors. Another technical consideration to minimize the receptor stimulation is the avoidance of cricoid pressure as it produces significant rise in heat rate and blood pressure than when cricoids pressure is not applied. Therefore it is necessary to weigh the risks and benefits before attempting this maneuver.

3. Topical anaesthesia

Spraying of topical lignocaine to the upper airway atleast two minutes before laryngoscopy can attenuate this hemodynamic response to a certain extent. On the other side, spraying in the upper airway by itself produces significant cardiovascular stimulation.

4. Regional nerve blocks

Glossopharyngeal nerve block at the tonsillar pillars and superior laryngeal nerve block at the greater cornua of the hyoid bone can obtund the sensory pathways from the oropharynx and the larynx.



5. Inhalational anaesthetics

Inhalational anaesthetics when administered in the dose range one minimum alveolar concentration (MAC) do only little to blunt this response to endotracheal intubation. Inordinately high doses of volatile anaesthetics (30% higher than the MAC for incision) is required to suppress this response but it does so only at the cost of producing severe cerebral vasodilatation and profound increases in intra cranial pressure (ICP) especially in patients whom the intracranial compliance is compromised.

6. Intravenous agents

With the exception of etomidate which maintains stable hemodynamics, all other agents like propofol, barbiturates and benzodiazepines cause profound cardiovascular depression at the doses required to suppress the intubation response.

7. Anaesthetic adjuvants

Opioids are one of the commonly used adjuvants to accentuate our relatively lighterplane of anaesthesia that are in routine practice. Fentanyl [12] which gives a graded response in suppressing this hemodynamic response doesn't achieve its peak CNS effect until 10 minutes after intravenous injection. Hence laryngoscopy and intubation are done in such a way so as to match the peak effect of these drugs in order to effectively minimize the stimulation of our cardiovascular system. IV

Lidocaine is another adjuvant used to attenuate the hemodynamic responses. While it is helpful in doses of 3mg/kg, at a lower dose of 1.5 mg/kg it does not seem to be good enough in attenuating this response for laryngoscopy and intubation.

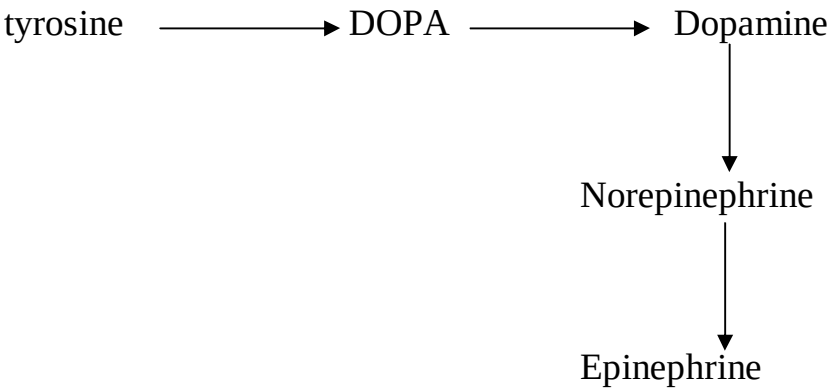
8. **Non anaesthetic adjuvant drugs**

Prophylactic use of vasoactive substances that have a direct effect on the heart also helps in bringing down the heart rate and blood pressure response to laryngoscopy and intubation. The agents that can be used are diltiazem, verapamil and nicardipine; hydralazine; nitroprusside; nitroglycerin; magnesium sulphate; metoprolol, labetalol, esmolol and clonidine

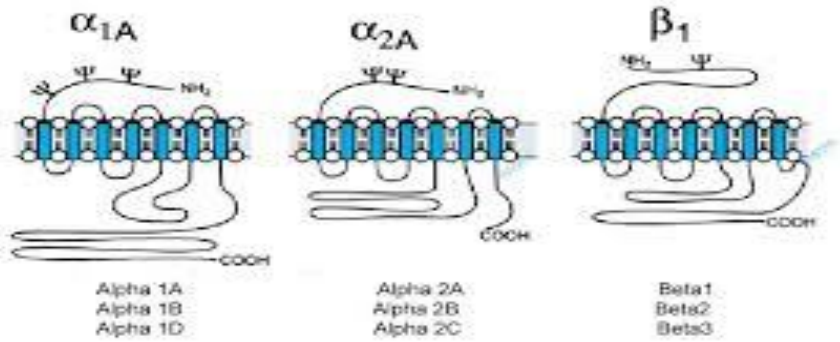
Almost all these drugs seem to be somewhat effective while comparing with placebo, especially when used in high doses. The optimal use of any of these agents is not defined well, although their use as adjuvants in high risk patients may be reasonable, with the warning that sufficiently larger doses are needed to attain the desired effect with some side effects, which warrants the assessment of risk benefit ratio. Esmolol[13] is one of the drugs best studied at a dose of 100 or 200mg which attenuated the cardiovascular response to endotracheal intubation, especially when combined with moderate dose opioid. Smaller dose of 1mg / kg had nil effect in suppressing the response to laryngoscopy and intubation.

GENERAL PHARMACOLOGY OF ADRENERGIC SYSTEM AND BETA BLOCKERS[13,14,15]

Catecholamines that are produced in our body are the endogenous catecholamines which include epinephrine, norepinephrine and dopamine. Aromatic amino acid tyrosine is the precursor for their synthesis. They are produce mainly in the adrenal medulla as epinephrine, in the sympathetic neurons as the norepinephrine which is a neurotransmitter for these neurons.



These substances act via alpha and beta adrenergic receptors. These receptors have further sub types in them as α1 predominantly in the blood vessels and vas deferens, α2 mainly in the pancreas and β1 in the heart mainly, β2 in the lungs abundantly and β3 predominantly in the adipose tissue.

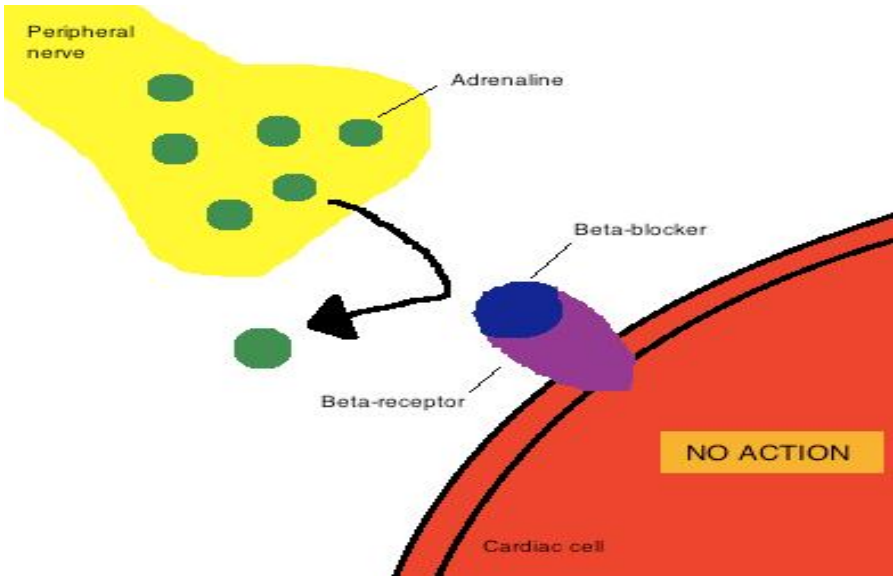


Why these receptors and catecholamines are important?? Ahlquist is the person who postulated the existence of beta adrenergic receptors,in 1948. These are the receptors through which the sympathomimetics will act to stimulate our sympathetic nervous system and maintain our hemodynamic homeostasis. Whenever there is excessive stimulation of the autonomic nervous system, this homeostasis gets disturbed and is unfavourable causing some adverse effects. So the need for adrenergic receptor blocker arises. As like α and β receptors, there are drugs available specifically to block these receptors. Ten years after Ahlquist postulation of the adrenergic receptors, adrenergic blocking agents were discovered.

Adrenergic blockers are the drugs which inhibit the binding of norepinephrine, epinephrine and other sympathomimetic drugs with alpha and beta receptors. Most of the drugs are acting as an antagonist in a competitive fashion. These drugs have been developed with different affinities for various receptors, so it is possible to interfere the response selectively that result from sympathetic stimulation. First generation beta

blockers also inhibit the β2 receptor in the bronchial smooth muscle leading to life threatening bronchoconstriction especially in asthmatics. Likewise it also masks the hypoglycemic symptoms in patients with diabetes. In order to have selective antagonistic action, specific blockers to β1 were developed. As there is no specific indication for blocking β2 receptors, β2 selective blockers were not developed clinically.

Beta -1 blockers block most actions of epinephrine and norepinephrine on the heart with less effect on beta -2 in bronchial smooth muscles and no effect on alpha receptors.



METOPROLOL[11,15]

A selective beta 1-adrenoreceptor blocking agent. It has neither intrinsic sympathomimetic activity nor membrane stabilizing activity.

PHARMACOKINETICS:

Well absorbed after per oral administration, reaching high concentration in the plasma after 1 to 3 hrs of ingestion.

Elimination half life: 3-4 hrs

METABOLISM & EXCRETION:

Bioavailability is relatively low because of first pass metabolism. It is extensively metabolized on liver, with little unchanged drug excreted in urine.

PHARMACODYNAMICS:

Effect on cardiovascular system – beta blockers has relatively little effect on the normal heart at rest, but has profound effect when sympathetic control of the heart is dominant, as during exercise or stress. The negative inotropic and chronotropic effect are by antagonizing the release of renin caused by the stimulation of the autonomic nervous system.

Beta receptor blockade will attenuate catecholamine induced activation of glucose metabolism and lipolysis. They decrease the effects of catecholamines on the determinants of myocardial oxygen consumption.

DOSE: 100mg/day (initial dose for treatment of hypertension)

ADVERSE EFFECTS:

Bradycardia, hypotension (due to overdosage), hypoglycemia (in diabetes patients), fatigue, cold extremities, mild sedation, vivid dreams (mainly with highly lipid soluble agents) and rarely depression.

DRUG INTERACTIONS:

Aluminium salts may decrease the absorption, drugs like phenytoin, rifampin and smoking stimulates the hepatic biotransformation

enzymes thereby reducing the concentration of beta blockers in the plasma. The bioavailabilities of metaprolol (also propanolol) are increased with cimetidine and hydralazine due to changes in the hepatic blood flow.

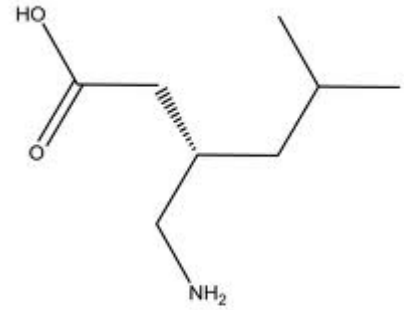
CONTRAINDICATIONS:

Heart rate <45 /minute

Heart block greater than first degree AV block

Caution in patients with bronchial asthma, diabetes mellitus

PREGABALIN



Pregabalin

(S)-3-(Aminomethyl)-5-methylhexanoic acid

PHYSICAL AND CHEMICAL PROPERTIES

S-(+)-3-isobutyl GABA, analogue of GABA

MECHANISM OF ACTION

It binds to α 2-delta subunit of calcium channels that exists in both central and peripheral nervous system. These channels are voltage dependent and are located presynaptically. The binding of this drug to this channel is perceived to be a reason for its action against both nociception and seizure activity. Once binded, they suppress the release

of several neurotransmitters like glutamate, norepinephrine, dopamine, serotonin, and substance P. All of them are excitatory neurotransmitters[16,17,18]. Pregabalin is inactive at GABA-aand GABA -b receptors.

PHARMACOKINETICS

ABSORPTION:

It is rapidly absorbed after oral ingestion in empty stomach, maximum plasma concentration occuring in one hour in the dose of 150mg/day. The volume of the distribution for per oral supplementation is around 0.56ml/kg and they are not protein bound. Bioavailability is more than 90% and is not dependent on the dose received. Although both gabapentin and pregabalin are gabapentinoids their absorption from the GIT is different. Gabapentin is absorbed through system L transporter, saturating the system producing non linear pharmacokinetics. However, the absorption of pregabalin is nonsaturable, producing linear kinetics[19]. Also there is three times higher absorption rate for pregabalin compared to gabapentin. All these factors contribute pregabalin to attain peak plasma concentration soon as one hour post dose.

ELIMINATION HALF LIFE:6.3 hours

METABOLISM AND EXCRETION:

Pregabalin undergoes negligible metabolism in humans. Methlypregabalin is the major metabolite of pregabalin. It is excreted unchanged in urine with the renal clearance of 73ml/minute.

PHARMACODYNAMICS:

This drug reduces the sensitization of dorsal horn neurons thereby reducing the onset of chronic pain. Rapidly crosses the blood brain barrier.Reduces the communication between the nerves and this effect makes it a good antiepileptic.

ROUTES OF ADMINISTRATION:

Oral tablets : dose:50-600 mg/day

ADVERSE EFFECTS / PRECAUTION:

Dizziness, drymouth, edema, reduced blood platelet counts, increased blood creatinine kinase levels, rhabdomyolysis, muscle pain, weakness.

CONTRAINDICATION: Nil, except hypersensitivity to the drug.

REVIEW OF LITERATURE

Nahidaghidai et al.,observed the cardiovascular response to orotracheal intubation using fibreoptic bronchoscope and direct laryngoscopy in patients for CABG undergoing general anaesthesia. Though intubating duration was less with direct laryngoscopy,there was no significant difference in BP or HR between two groups and was concluded that FOB was not superior in attenuating the intubation response.

Manjunath et al., -blunting of hemodynamic response to intubation using direct laryngoscopy with lignocaine spray of 10%. The study was concluded with the result that use of single metered dose of lignocaine spray 10% 3-5 minutes before induction is helpful in decreasing the pressor response.

Ushasaha et al[23].,- Pressor response and hypertension. The study was carried with 128 hypertensive patients planned for elective surgery under general anaesthesia to assess the stress response for laryngoscopy and intubation. Earlier the concept of withholding the antihypertensive medication prior to a planned surgery was there because of the thought that continuation of antihypertensive is more dangerous than the hypertension itself. But now there are evidences that suggest continuation of the drugs in the perioperative period is advantageous. There is a pressor response occurring to laryngoscopy and intubation due to

sympathetic stimulation in normal individuals itself. In case of patients with hypertension the sympathetic system is highly sensitized so there is an exaggerated pressor response to laryngoscopy and intubation. So the risks for complications are high which necessitates some techniques or pharmacological agents for blunting such response.

Fauzia khan et al., - Pharmacological drugs for preventing morbidity associated with pressor response of intubation. This study was carried with the background that several drugs were used to decrease or blunt the cardiovascular response to intubation. The changes produced were of not concerned much in otherwise normal individuals but causes some mortality and morbidity to high risk patients. Taking around 72 RCT's in this analysis it was concluded that risk of arrhythmia occuring with intubation was much lessened with administration of local anasthetics, beta blockers,calcium channel blockers and opioids when compared with placebo. Also there is a reduction in the evidence of ischemia in the ECG.

L.Saarnivaara et al [24].,- Effects of practolol and metoprolol on QT interval, blood pressure and heart rate during anaesthetic induction. Practolol with intrinsic sympathetic activity and metoprolol without this activity are used. Normally during induction with thio, after suxamethonium and after intubation there is QT interval prolongation. Use of practolol 100µg/kg reduces the QT prolongation after

suxamethonium. Metoprolol of 20, 30 and 40 µg/kg reduces the QT prolongation after thiopentone and after suxamethonium but not after intubation. Neither of them prevented the cardiovascular response to intubation effectively with such low doses. Only the occurrence of ventricular ectopics got reduced with increasing doses of metoprolol. As both the drugs reduced the QT prolongation with suxamethonium, they suggest that occurrence of QT prolongation after succinyl choline is mediated via activation of sympathetic nervous system.

Pristautz H et al., - Effect of premedication with beta adrenolytic in hemodynamic parameters and free fatty acid levels during oesophago – gastro – duodenoscopy. Three groups of patients were taken and given bunitrolol, hyoscine n butyl bromide with diazepam and last group without any drug. The rise in heart rate and systolic BP was significantly less with patients received bunitrolol and also the occurrence of premature beats. In conclusion, a pre medication with beta adrenolytics could be useful in patients with labile hypertension, autonomic dysregulation and hyperkinetic heart syndrome.

Derbyshine et al [25].,- Response in plasma catecholamine level to tracheal intubation. In this study, measurement of plasma adrenaline and noradrenaline were taken during induction of anaesthesia and tracheal intubation subsequently. There were increase in both the catecholamines

and increase of mean arterial pressure in both the groups who received either succinyl choline or pancuronium for intubation. But there was a significant correlation exists between MAP and catecholamine level in patient received suxamethonium. Moreover blood samples were taken from central and peripheral venous access and arterial sites simultaneously, maximum change occurred in central venous sample.

Martin donald et al [26].,- Blunting the cardiovascular response to intubation with low dose fentanyl. The study was carried out with fentanyl 8mcg/kg along with thiopentone 3mg/kg and the other group receives thiopentone 6mg/kg for induction of anasthesia. It was found that this dose of fentanyl is sufficient enough in blunting the postintubation hypertension when used as an adjuvant and the risk for developing postoperative respiratory depression is less.

L.Landgren et al., -Hemodynamic response and QT prolongation in ECG after succinyl choline facilitated intubation in children during induction – a dose related attenuation by alfentanil[20]. Normally tracheal intubation is associated with rise in HR, BP and catecholamines. Also there will be QT prolongation and occurrence of arrhythmia in some individuals. This QT prolongation occurred mostly in individuals who were given suxamethonium. The reason seems to be due to increased plasma noradrenaline level which occurs after administration of succinyl

choline. It has been already established that fentanyl 6µg/kg will abolish catecholamine related hemodynamic changes for intubation[21]. Alfentanil 13.5µg/kg attenuates and 75µg /kg abolish the response completely for intubation in adults[22]. But the effective dose to use in children for attenuating the effects of succinyl choline the present study was done with three different doses of alfentanil(10, 25 and 50 µg.kg). In conclusion, 25µg/kg of alfentanil is found to be ideal in preventing the stress response to intubation and QT prolongation.

Matthew D.Mullet et al.,- Tactile stimulation of the oropharynx causes excitation of the sympathetic system in conscious individuals. Stimulation of the oropharynx will cause the gag reflex and raise the heart rate and the blood pressure whether the individual is conscious, sedated or anaesthesized. This is because of the interaction between the defense reflexes in the upper airway and the autonomic nervous system. These airway reflexes (cough reflex, swallowing reflex and gag reflex) are practicable under normal situations and they correctly direct the air and food in their right passage. During any acute perturbation like choking, coughing and tactile stimulation of the oropharynx, there will be rise in HR,BP and the homeostasis is likely to be affected. The same thing happens during laryngoscopy, broncoscopy and intubation thereby increasing the myocardial oxygen demand posing the patients to the risk

of myocardial ischemia and arrhythmia. So the need to blunt the increase in HR and BP during such manoeuvres received much attention. The study was done with a purpose to establish the integrated neurovascular response to oropharygeal stimulation in conscious patients and to blunt the response of the upper airway to local anaesthetics. The study was concluded with the result that any stimulation of the afferents in the oropharynx causes an acute rise in heart rate, blood pressure and constriction of the renal vasculatures.These outcomes can be abolished by using local anaesthetics to the upper airway.

Jakobsen CJ et.al [27] Effect of metoprolol given before surgery on cardiovascular system, catecholamine response and bleeding during hysterectomy.

This study was carried out with metoprolol 100mg or placebo given orally before anaesthesia and observed that oral premedication with metoprolol attenuates the hypertensive response to tracheal intubation and reduces both arrhythmia and operative blood loss.

Poupak Rahimzadeh et al[28]**.,**Effects of Premedication with Metoprolol on Bleeding and Induced Hypotension in Nasal Surgery

Patients undergoing nasal surgery are divided into 4 groups and were given 50 mg metoprolol on the night before the day of surgery, 50 mg metoprolol on the day of surgery, 50 mg metoprolol on the night before

surgery and on the day of surgery and placebo. Following preparation of the patient on the operating table, pulse rate, systolic and diastolic pressures were recorded after intubation and throughout the surgery.

This was concluded with that, using the double dose of metoprolol causes significant reduction in intraoperative bleeding and improves the operative field visibility thereby increasing surgeon's level of satisfaction and also it reduces the patient's level of distress in the recovery room. Distinctly, in order to blunt our cardiovascular response and decrease the catecholamine level related to surgical stress, giving higher or frequent doses of metoprolol are needed. In other words, to maintain the hemodynamics of the individual for head and neck surgeries with less stress and less bleeding, use of metoprolol have positive impact on thecardiovascular system and achieves a desired response in blood pressure and heart rate.

Issursingh et al.,In this study they compared oral metoprolol with intravenous lignocaine for decreasing the cardiovascular stress response to laryngoscopy and intubation. Oral metoprolol 50 milligram given 2 hours and I.V lignocaine 1.5mg/kg given 2 minutes before induction of anaesthesia and concluded that 1.5mg /kg IV lignocaine is ineffective in decreasing the intubation response while oral metoprolol attenuates the pressor response significantly.

Kumar M et al., -Metoprolol for blunting of hemodynamic response to laryngoscopy and intubation. In this study , 60 patients divided into 30 in each group were given normal saline for one group and 3 mg of metoprolol for another group five minutes before induction of anesthesia and observed that metoprolol attenuated the cardiovascular stress response effectively with clinically significant difference.

Carl johan et al., -Reduction in the occurrence of atrial fibrillation after thoracotomy for lung resection with perioperative metoprolol. This study was done with an objective to evaluate the effectiveness of oral perioperative β blockade in reducing the frequency of atrial fibrillation because of the association of more chances of atrial fibrillation in thoracic surgeries mainly due to increased sympathetic action. The patients were given either 100mg metoprolol or placebo before surgery and once daily postoperatively. The study was concluded that perioperative β blockade reduced the occurrence of atrial fibrillation without any serious adverse effects as AF causes increase in oxygen consumption and cardiac index post surgery.

Korpinen R et al[29]., -Comparing the effects of alfentanil and esmolol over QT interval in ECG, pulse rate and blood pressure during induction of anaesthesia. Thestudy was carried out with two different doses of esmolol(2mg/kg and 3mg/kg) and alfentanil (0.03mg/kg). Esmolol[13] is

effective in preventing the QT prolongation after suxa and thiopentone but not after laryngoscopy and intubation. Whereas alfentanil did so after succinyl choline, thiopentone and laryngoscopy, but not after intubation. Both the drugs do not prevent the increase in HR,BP occurring with laryngoscopy and intubation. With 3mg/kg of esmolol, there is no incidence of cardiac arrhythmias but occurred in other groups.

Sarveshsingh et al., - Comparison of low dose esmolol and labetalol for decreasing the sympathomimetic response to intubation. They concluded that labetalol (0.25mg/kg) is better than esmolol (0.5mg/kg) in producing significant decrease in the response but bradycardia occurs more with labetalol.

Jakobsen CJ et.al studied the impact of preoperative metoprolol for improving the cardiovascular stability and reducing the oxygen consumption after thoracotomy.

This study was done to know the hemodynamic effect of preoperative beta blockade in and around the time of surgery and its impact on the hemodynamic variables of the surgical stress response. This study was done with the background that increased activation of the sympathetic system and its cardiovascular changes during surgery play a vital role in producing the complications. Though blockade of the autonomic, motor and somatic system high in the thoracic regionreduces

the sympathetic response with excellent pain relief, hemodynamic and endocrine response is still present. In situations like this, beta adrenergic blockade will be effective.

The study was concluded with the result that the preoperative beta blockade during combined procedure of general anaesthesia and high thoracic epidural block stabilized the perioperative heart rate, cardiac index and reduced the total oxygen utilisation.

A.J.Coleman et al[30]., - Evaluation of cardiovascular response to anaesthesia using two different doses of intravenous metoprolol and placebo. With 15 patients in each group, first group received I.V placebo, second group got 2 mg metoprolol and 4 mg for the third group. The study was concluded with the result that both 2 mg and 4 mg doses of metoprolol effectively reduced the increase in heart rate and blood pressure without any significant difference and was also found that metoprolol as very effective antiarrhythmic drugs.

Mikawa et al [31].,they did a comparative study between nicardipine, diltiazem and verapamil(calcium channel blockers)[32] for reducing the pressor response to intubation and concluded that though these drugs decreases the hypertensive response, failed to inhibit the rise in catecholamines and even there was an increase in these level with nicardipine for intubation.

ElifBengiSener et al[33]., -Conventional laryngoscopy versus intubating laryngeal mask airway – upper airway morbidity and cardiovascular response in patients with hypertension. The time taken for intubation was longer with intubating mask airway than direct laryngoscopy. Thus there is repeated and intense stimulation of the oropharynx and trachea with ILMA (intubating laryngeal mask airway), thereby undesirable hemodynamics more than with direct laryngoscopy. In conclusion that the ST segment changes and morbidity related to upper airway stimulation are similar in both techniques of intubation, direct laryngoscopy which is safe and rapid to perform is preferred in patients with hypertension having normal airway.

Ushabafna et al[34].,they did a comparative evaluation of different doses of gabapentin to blunt the hemodynamic response to laryngoscopy and intubation. The drugs were given one hour prior to surgery and significant decrease in MAP and HR was observed with the group given 1000mg of pregabalin when compared to 600mg. The response is found to be dose dependent.

Eren et al[35]., - Evaluated the effectiveness of pregabalin in suppressing the hemodynamic response to tracheal intubation in lumbar spine surgeries. This drug was identified by Chemist Richard Silverman. The FDA approved it for treating epilepsy, pain associated with diabetic

neuropathy and postherpetic neuralgia. Furthermore, evidence suggests that giving this drug during the time of surgery is effective for providing preoperative anxiolysis, prevention of chronic pain, nausea and vomiting after surgery and delirium. Also it was found to be helpful in attenuating the cardiac response to laryngoscopy and intubation.

D.Memis et al [36]., -various doses of gabapentin for blunting the response occurring for laryngoscopy and intubation. In this study oral placebo, two different doses of gabapentin (400mg and 800mg) one hour prior to intubation and was found that 800mg gabapentin is effective in suppressing the pressor response comparatively with significant decrease in heart rate and blood pressure.

AmaniA.Ali et al.,They evaluated the two various doses of gabapentin on cardiovascular stress response and intraocular pressure occurring for laryngoscopy and intubation. The patients were divided into three groups with 20 in each. They were given oral placebo, 800mg gabapentin and 1200mg gabapentin 2 hours before surgery respectively. Intraocular pressure, heart rate and arterial pressure were measured and found that 1200mg gabapentin doesn't cause any rise in HR, MAP and IOP for intubation and they were below the baseline till ten minutes of the procedure. While with 800mg gabapentin, there was a rise in the measured parameters and that returned to baseline within five to ten

minutes of the intubation. Thus it was concluded that 1200mg gabapentin is very effective in preventing the occurrence of stress response than 800mg dose of the drug.

Cory toth et al., - latest safety evidence and clinical implications of pregabalin for the treatment of neuropathic pain.Pregabalin is a gabapentinoid initially developed for the treatment of epilepsy and also used for the treatment of neuropathic pain. It is associated with mild CNS side effects and systemic adverse effects. This article discusses the potential use of the drug and its side effects like sedation, dizziness, dry mouth and peripheral edema. This also elaborates about the clinical implications of pregabalin.

Howard N.Bockbrader et al., -Evaluation of the pharmacological kinetics and dynamics of pregabalin and gabapentin. Oral gabapentin takes atleast 3 hours to attain peak plasma concentration and it follows zero order kinetics, so its kinetics is less predictable. Whereas pregabalin reaches peak concentration in the plasma within an hour, its absorption follows first order kinetics with bioavailability >90%. In conclusion, pregabalin found to have distinct pharmacokinetic profile, thereby improved pharmacodynamic effect.

Namratha et al.,They did a comparative evaluation between oral gabapentin and pregabalin for reducing the pressor response to tracheal

intubation. This study was a double blind placebo controlled study with 90 adult patients of ASA I and II with 30 in each group receiving placebo, 800 mg of gabapentin and 150 mg of pregabalin respectively and vital parameters were recorded.The result was that though there is significant raise in HR and MAP in control group after scopy, pregabalin is more sedative and better than gabapentin in suppressing the pressor response.

Rastogibhawan et.al [37].,This study was done with an aim to find the clinically safe and useful dose of pregabalin as premedicant for decreasing the hemodynamic pressor response to airway instrumentation during general anesthesia. This study was carried out with two different doses of pregabalin of 75mg and 150mg and concluded that the pressor response decreased in a dose dependent manner and all the patients were stable hemodynamically throughout the intraoperative period without prolongation in recovery time.

Talikoti A T et al., - Comparison of intravenous preservative free lignocaine (1.5 mg/kg) with pregabalin 150 mg orally for blunting the response to laryngoscopy and endotracheal intubation. Two groups of patients are selected and given oral pregabalin 150mg 3 hours before intubation or I.V. lignocaine 1.5mg/kg 3 minutes prior to laryngoscopy and parameters were recorded before induction as baseline and at 1,3,5

minutes following laryngoscopy. After obtaining all data's and statistical analysis, it was concluded that lignocaine is more effective for controlling the rise in pulse rate whereas pregabalin is effective in controlling the diastolic blood pressure and mean arterial pressure following laryngoscopy.

Aftab Ahmad Khan et al.,-comparative study evaluating the effectiveness of oral clonidine and pregabalin on decreasing the effects of laryngoscopy and intubation. The study was carried out with 300µg clonidine for group 1, 75mg pregabalin for group 2 and placebo to group 3, 120 minutes prior to surgery. In conclusion clonidine 300µg was superior in maintaining the hemodynamics during intubation with adequate sedation and pre op anxiolysis without increasing the recovery time and adverse effects.

Snehalatha Bhashyam et al., This study was carried out to compare the efficacy of gabapentin and pregabalin as a premedicant for providinganxiolysis, sedation and attenuating the pressor response to endotracheal intubation. Both gabapentin 600mg and pregabalin 150mg given 1 hour before surgery decreased preoperative anxiety, provides good sedation and effectively attenuates the response for intubation. But when comparing both, pregabalin led to a better effect without significant side effects.

Ali et al.,Demonstrared that gabapentinoids administration does not affect the basal catecholamine concentrations in the plasma before intubation, failed to attenuate the catecholamine response to intubation and conversely, enhanced the norepinephrine level in the plasma. The results of this study also revealed that despite higher norepinephrine levels in the plasma in patients received gabapentin than the control group, the rise in mean arterial pressure and heart rate was lower in gabapentin group.

Rakeshkumarsingh et al., A case report – pregabalin in post traumatic neuropathic pain. Use of pregabalin in patients with peripheral neuropathy in doses starting from75mg, once a day for a week and then gradually increasing to 150mg, twice a day. After three months follow up, the patients had complete relief of pain. From this it is clear that pregabalin is effective in providing pain relief for central and peripheral neuropathies. This study found out the effectiveness of pregabalin in the treatment of nerve injury after trauma not responding to regular analgesics.

Harun Aydogan et al., -Addition of 75 mg pregabalin reduces the pain scores and opioid consumption in adults undergoing percutaneous nephrolithotomy. Two groups of patients were enrolled and were given pregabalin or the placebo. Patient’s pain was analysed with visual analog

scale, postoperative opioid consumption during first 24 hours after surgery and Serum neutrophil gelatinase – associated lipocalin (NGAL) measured before and after surgery at 2^{nd} and 24^{th} hour. This study was concluded with the result that single preemptive dose of 75mg is effective in attenuating the pain scores and reduce the total analgesic consumption without causing any hemodynamic instability and adverse effects.

Ayyasyamasundar et.al[38] (2012) in their study observed the effectiveness of preemptive Pregabalin on attenuation of stress response to endotracheal intubation and opioid sparing effect in patient undergiong off pump coronary artery bypass grafting.

It was a randomized, double-blind, placebo-controlled, efficacy study. It was a comparison between two groups of 30 each adults. . In the control group, the patients were given placebo capsules and in the pregabalin group, the patients were given pregabalin 150mg capsule one hour prior to the surgery. The patients were compared for haemodynamic changes before the start of surgery, after induction,1, 3 and 5 minutes after intubation.

They concluded that single oral dose of 150mg pregabalin given 1 hour before surgery suppresses the reflex tachycardia and hypertension related to laryngoscopy and intubation; the analgesic and opioid sparing effect of pregabalin given as a premedicant was not apparent and it does not

produce dizziness and visual disturbances. Moreover, this postoperative delirium is one such complication that patients undergoing cardiac surgery are at increased risk of developing it. So preoperative use of pregabalin in these patients for inhibiting the pressor response is also helpful in decreasing the incidence of postoperative delirium.

Gupta et al [39]., - Premedication with pregabalin – a new option for maintaining hemodynamic stability during general anaesthesia. Use of laryngoscope, intubation and pain are such notorious stimulus that will disturb the hemodynamic homeostasis. Appropriate premedication, smooth induction and intubation are very important inorder to maintain the homeostasis. With this context in mind, pregabalin 150mg was given an hour prior to surgery and was found to have good sedation and effective analgesia with significant attenuation of the deleterious and adverse hemodynamic pressor effects.

Kumkumgupta et.al[40].,did a comparative evaluation of oral premedication with Pregabalin or Clonidine for haemodynamic stability during laryngoscopy and laproscopic cholecystectomy.

A total of 180 healthy adult patients of age 35 to 52 years with ASA Grade 1 and 2 were randomized to receive placebo(Group 1), Pregabalin 150mg(Group 2), or Clonidine 200 micrograms(Group 3), given 75 to 90 minutes before surgery as oral premedication. The groups were compared

for preoperative sedation, changes in heart rate, mean arterial pressure prior to premedication, before induction, after laryngoscopy.

They concluded that both Pregabalin and Clonidine have sedative and anxiolytic effects as oral premedicants and decreased the need of intraoperative analgesic drug requirement. Clonidine was superior to Pregabalin for the attenuation of the haemodynamic responses, but the incidences of intra operative and post-operative bradycardia were high with clonidine. There were no post-operative side effects and no significant differences in the parameters of recovery between the two groups.

Ebrusalman et.al[41].,in their study evaluated the efficacy of pregabalin as a premedicant to attenuate the cardiovascular response to laryngoscopy and tracheal intubation. Two groups of patients were allocated and one received placebo and the othergroup received pregabalin 150mg one hour prior to surgery. In conclusion its found that premedication with single dose pregabalin 150mg attenuates Hemodynamic Response to laryngoscopy and intubation.

Archana K did a comparison with oral pregabalin and clonidine for blunting the intubation response with 150mg and 200µg respectively in two groups of patients of 30 in each. In conclusion, both the drugs are effective in attenuating the hemodynamic response to intubation.

Pregabalin is better in attenuating the pressor response and clonidine is effective in blunting the tachycardic response.

PreethaElizabath George et al[42]., - Dilemmas in premedication – is pregabalin the answer? The study was done with two groups receiving placebo or 150 mg pregabalin orally, 1.5 hrs prior to surgery. The vital parameters were recorded at baseline and at 1, 3, 5 and 10 minutes after intubation. After intubation the hemodynamics were found to be more stable in the pregabalin group. Thus it was concluded that premedication with pregabalin is effective in obtunding the cardiovascular response to intubation.

Victoria Faria Baln and Normand A.G.,In their article, complications of tracheal intubation have classified the neurogenic or reflex mediated complication into three different categories.

i. Laryngeal reflexes

Spasm of glottis, bronchospasm, apnoea, bradycardia, dysrhythmia and hypotension can occur. The mere presence of the tracheal tube seems to be the most common cause of bronchospasm in anaesthetized asthmatic patients.

ii. Laryngo-sympathetic reflexes

Tachydysrhythmia, acute arterial hypertension and a hyperdynamic state can occur. It is related to the increased production of nor-adrenaline.

iii. Laryngospinal reflexes

Coughing, vomiting and bucking may occur.

Stoelting[43] recommended that attempt should be made to attenuate the pressor response to laryngoscopy and tracheal intubation when the laryngoscopy time is likely to be more than thirty seconds. When laryngoscopy is prolonged, laryngotracheal rather than intravenous Lidocaine is necessary for attenuating the circulatory responses to intubation.

AIM OF THE STUDY

To compare the effectiveness of metoprolol and pregabalin, for attenuation of cardiovascular response to laryngoscopy and tracheal intubation.

Objective:

To study the hemodynamic parameters like

1.Systolic pressure (SBP)

2.Diastolic pressure (DBP)

3.Mean arterial pressure (MAP)

4.Heart rate (HR)

MATERIALS AND METHODS

STUDY DESIGN:

This study is a randomized prospective study to study the effectiveness of metoprolol and pregabalin. This study was conducted in Govt. Kilpauk medical college Chennai from March 2015 to August 2015

STUDY SETTING AND POPULATION

After getting approval from institutional ethical committee, 90 patients of either sex aged from 20 to 45 years scheduled for various elective surgeries under general anaesthesia were enrolled in the study. All of them required orotracheal intubation as part of their anaesthetic management and gave written informed consent to participate in the study.

INCLUSION CRITERIA:

1) Patients in 18 - 45 years of age
2) Body weight (45 – 70 kg)
3) Patients who undergo surgery requiring General Anaesthesia under ASA Physical Status 1 and 2.
4) Elective surgery.

EXCLUSION CRITERIA:

1) Mallampati score >3
2) Morbid obesity

3) Drug allergy

4) End stage liver / renal disease

5) Patient refusal

6) Known asthmatic / COPD patients

7) Hypertension

8) Diabetes Mellitus

9) Epilepsy

This study was designed to study the effectiveness of the two drugs Metoprolol and Pregabalin in attenuating the responses to laryngoscopy and intubation. The two drugs were compared in terms of their effects on heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure.

All patients were assessed pre operatively by history, physical examination, routine laboratory tests, chest X-ray and electrocardiogram. A pre operative visit was made to allay the anxiety and to develop a good rapport. The patients were instructed to fast overnight and aspiration prophylaxis was advised with Tab. Ranitidine 150 mg and Tab. Metoclopramide 10 mg which were given on the night before surgery

On the day of surgery the patients were examined in the waiting room and the pulse rate(PR), systolic blood pressure

(SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) was recorded as preoperative value.

The patients were then randomly assigned into three groups of 30 each: Group A, Group B and Group C.

Group A – patients were given 100mg metoprolol one hour prior to intubation.

Group B – patients were given 150mg pregabalin one hour prior to intubation.

Group C – patients were given placebo one hour prior to intubation.

An 18 gauge intravenous cannula was placed and crystalloid infusion was started. The rate of infusion was as per the Holliday-Segar rule. All patients were premedicated with Inj.Ranitidine 150mg and Inj.Emeset 4mg I.V. Half an hour later patients were given Inj.Glycopyrrolate 0.005 mg/kg IV, Inj.Midazolam 0.05mg/kg IV.

On arrival in the operating room, Patients were monitored with a non invasive monitor. The parameters that were monitored include heart rate, blood pressure, oxygen saturation and electrocardiogram.

All patients received fentanyl 0.02 mg/kg IV in the operating room. Then induced with Inj.propofol 2mg/kg IV and

Inj.vecuronium 0.5mg/kg was given to achieve muscle relaxation. Controlled positive pressure ventilation was done with 100% oxygen using bag and mask. A direct laryngoscopy was done 3 minutes after the injection of the muscle relaxant and the patients were intubated with appropriate size cuffed endotracheal tube.

All patients who strained or laryngoscopy took more than 15 seconds or a second attempt was required and patients in whom the surgical procedure lasted for more than three hours were excluded from the study. Heart rate , blood pressure (systolic, diastolic, mean arterial pressure) were recorded at the first, second, third, fifth and tenth minute following intubation and was recorded as T0, T1, T3, T5 and T10 respectively. All patients were ventilated using oxygen and nitrous oxide mixture in the ratio of 40%: 60%. Muscle relaxation was maintained with additional doses of Inj.Vecuronium 0.02mg/kg.

Intraoperatively the heart rate, blood pressure, oxygen saturation, ECG was continuously monitored in all the patients. At the end of surgery, neuromuscular paralysis was reversed with Inj.Neostigmine 0.04mg/kg IV and Inj.Glycopyrrolate 0.01mg/kg IV. Patients were extubated after thorough oral suctioning. The patients were then shifted to the post operative ward and observed for upto 24 hours.

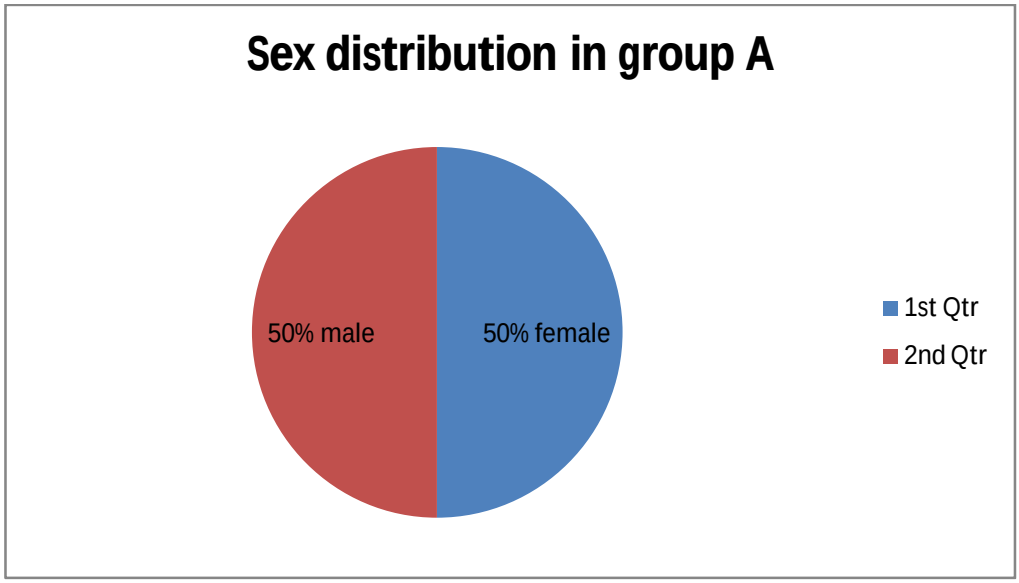
The results were systematically analyzed using one way ANOVA and Chi square test. The software used for analysis of the data was SPSS version 20 for windows. A P-value of less than 0.05 is considered to be statistically significant and P-valve less than 0.01is considered as highly significant.

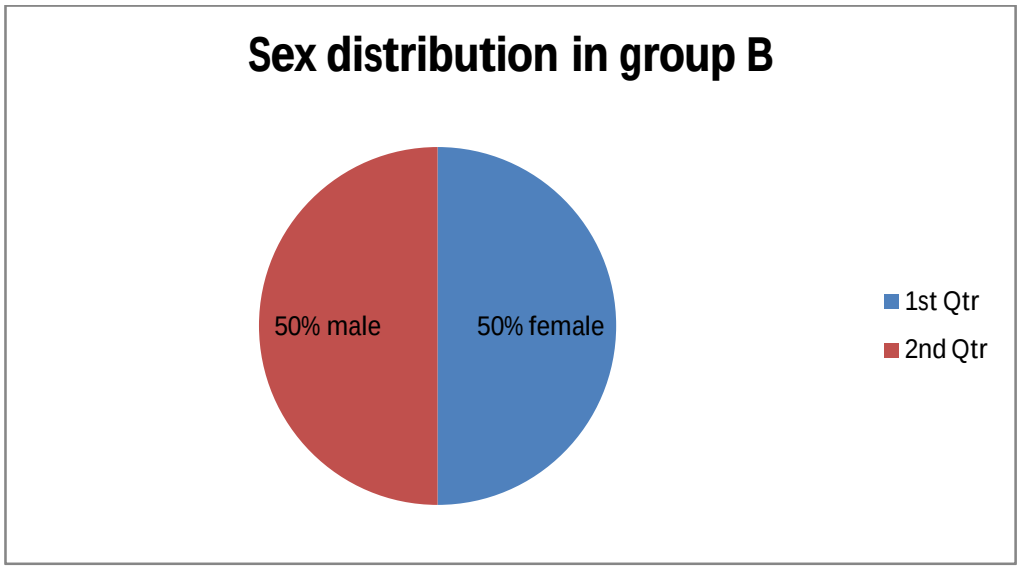
OBSERVATION AND RESULTS

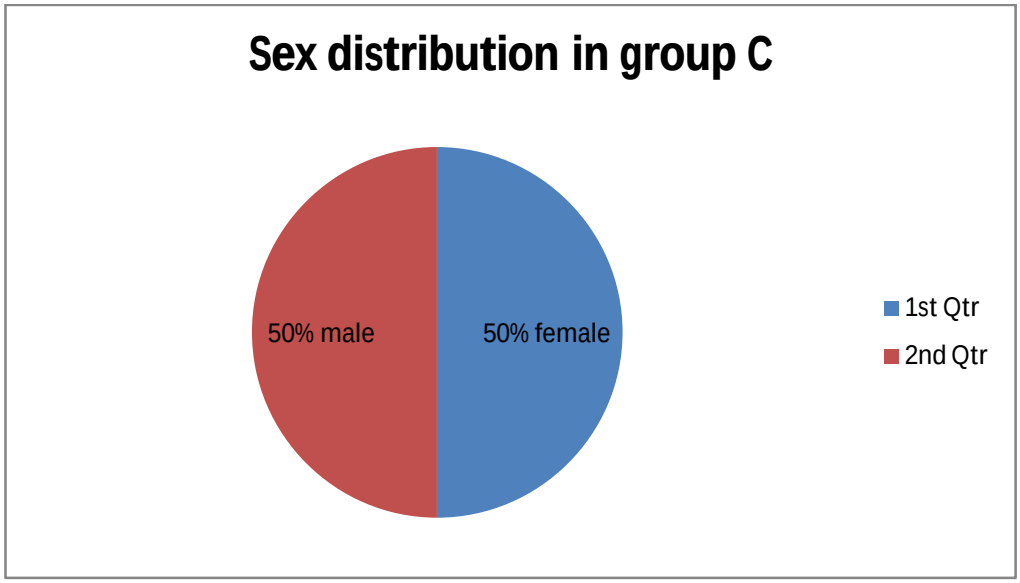
A total of ninety patients were studied in this study. Thirty patients were enrolled into group A, thirty patients into Group B and thirty patients into group C. There was no statistical significant disagreement between the two groups when the parameters like age distribution, sex distribution, weight and height of the patients and MPC classification were compared.

Table 1: Sex distribution in each group

Group		Sex		Total
		male	female	
Group A	No of patients	15	15	30
	% within group	50%	50%	100%
Group B	No of patients	15	15	30
	% within group	50%	50%	100%
Group C	No of patients	15	15	30
	% within group	50%	50%	100%
Total		45	45	90
		50%	50%	100%


Sex distribution in group A
50% male
50% female
1st Qtr
2nd Qtr

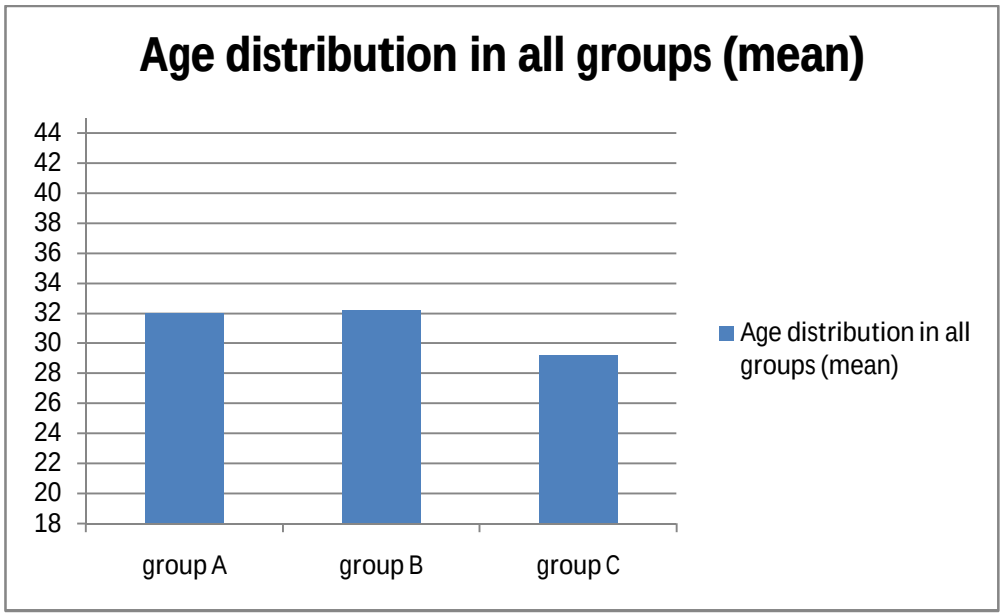

Sex distribution in group B
50% male
50% female
1st Qtr
2nd Qtr



Sex distribution is comparable between all the three groups.

Table 2: Age distribution in each group

	Group A	Group B	Group C
Average age (in yrs)	32	32.2	29.2



Age distribution between the three groups is comparable.

Table 3: Preop vital parameters

	Group A	Group B	Group C	P
HR(beats/min)	79.9±4.84	88.7±11.4	84.8±11.5	0.004*
SBP (mmHg)	122.1±5.17	122.7±13.9	112.4±10.4	0.000**
DBP(mmHg)	80.6±5.4	79.8±10.01	74.06±6.48	0.002*
MAP(mmHg)	94.2±4.69	94.46±10.8	87±6.81	0.000**

Chart for pre operative parameters

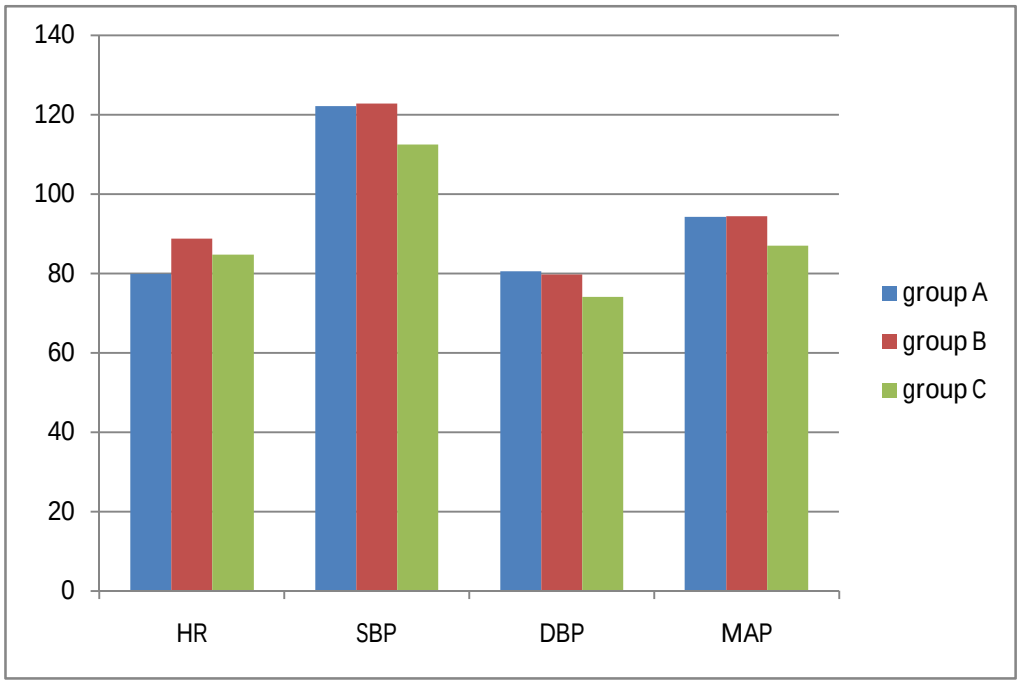


Table 3: preinduction vital parameters

PI	Group A	Group B	Group C	P
HR(beats/min)	80.9±6.67	85.9±11.58	84.53±8.72	0.107
SBP (mmHg)	108.5±10.08	108.06±8.67	117.63±7	0.000**
DBP(mmHg)	70.03±8.51	70.9±6.78	78.6±6.04	0.000**
MAP(mmHg)	82.6±8.73	83.3±6.30	92.7±7.00	0.000**

Chart at preinduction:

Table 3: Parameters at the time of induction

T0	Group A	Group B	Group C	P
HR(beats/min	80.5±8.05	98.16±9.80	106.4±14.4	0.000**
SBP (mmHg)	106.8±12.3	119.13±17.12	118.5±20.89	0.010*
DBP(mmHg)	72.4±10.56	77.6±14.08	81.8±16.38	0.035*
MAP(mmHg)	83.7±10.5	91.4±14.74	93.8±17.56	0.024*

Chart at the time of induction:

1.At the time of induction, heart rate in group A is less than that of group B which is less than that of group C.

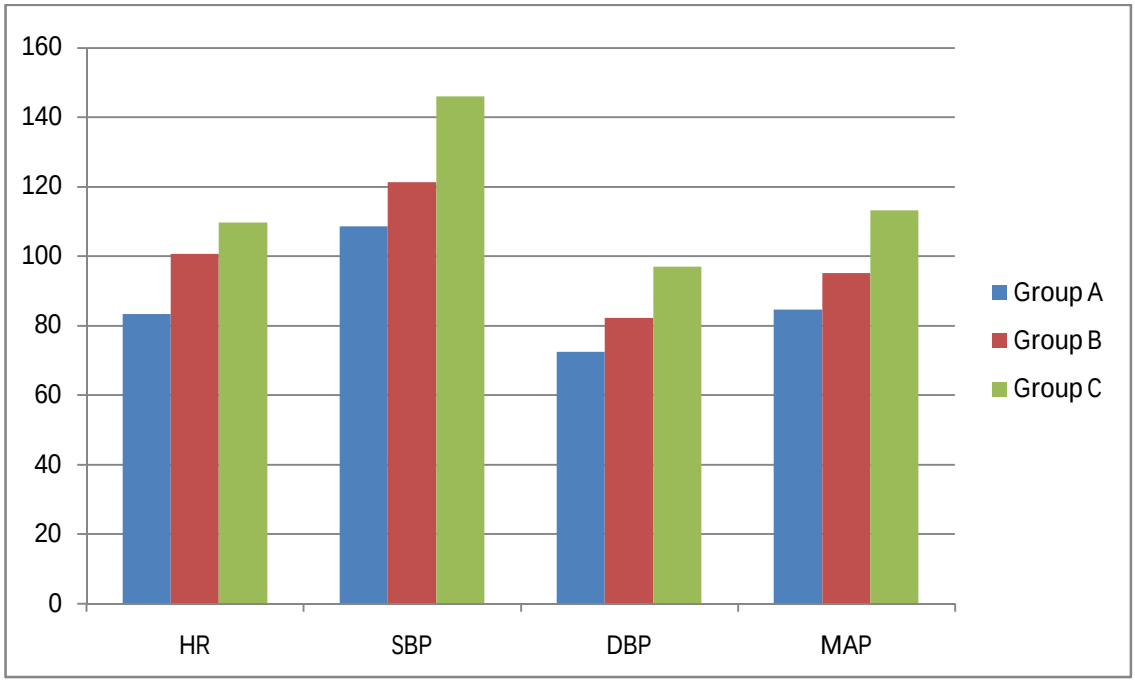
2.With regards to systolic and diastolic pressure at this induction time, group A has less value than group B and C, which are almost similar.

Table 4:Parameters at first minute

T1	Group A	Group B	Group C	P
HR(beats/min)	83.4±6.6	100.6±10.25	109.7±10.77	0.000**
SBP (mmHg)	108.6±13.12	121.3±12.9	146±13.96	0.000**
DBP(mmHg)	72.5±8.8	82.2±9.49	96.9±10.75	0.000**
MAP(mmHg)	84.6±9.7	95.1±10.10	113.2±10.98	0.000**

Data were expressed as mean ±SD

Parameters at the first minute :



At first minute after intubation, heart rate is less in groupA than in group B which is less than in group C.

The difference in blood pressure is also significant that patients in group A has less rise in blood pressure than that in group B and C.

Table 5: Parameters at third minute

T3	Group A	Group B	Group C	P
HR(beats/min)	80.1±5.82	96.46±11.5	104.66±11.49	0.000**
SBP (mmHg)	105.2±13.06	114.2±11.96	135.83±12.20	0.000**
DBP(mmHg)	70.1±8.45	73.9±9.60	88.7±11.61	0.000**
MAP(mmHg)	81.7±9.65	87.1±9.27	104.06±11.31	0.000**

Data were expressed as mean ±SD

** Means there was a highly significant difference in HR between three groups (P <0.01)

Parameters at third minute:

At third minute after intubation, rise in heart rate is insignificant in group A than in group B and C.

The heart rate in group A becomes comparable to the preoperative heart rate at this third minute but this is not so in group B and C.

The blood pressure and mean arterial pressure in group A is significantly less than that of in group B and C and these values are less in group A and B when compared with their preoperative values but not in group C.

Table 6: Parameters at fifth minute

T5	Group A	Group B	Group C	P
HR(beats/min)	76.0±6.65	88.1±8.57	96.2±9.15	0.000**
SBP (mmHg)	108.3±12.3	110.7±11.59	118.8±13.81	0.005*
DBP(mmHg)	70.4±6.75	72.3±8.49	81±12.73	0.000**
MAP(mmHg)	82.9±8.3	85.3±8.76	93.5±12.8	0.000**

Data were expressed as mean ±SD

* Means there was a significant difference in HR between the three groups ($P<0.05$)

** Means there was a highly significant difference in HR between three groups ($P <0.01$)

Mean Parameters at fifth minute:

At fifth minute after intubation, the heart rate doesn't rise in group A, even less than the preoperative value of that group; in group B the rise is insignificant and is comparable with the baseline value in that group; but in group C there is a rise which is significant.

With regards to blood pressure and mean arterial pressure, there is no significant rise in group A and B.

Also in group B, the blood pressure and mean arterial pressure becomes comparable to their baseline values at this minute.

In group C it is much more than its preoperative value and is significant.

Table 7: Parameters at tenth minute:

T10	Group A	Group B	Group C	P
HR(beats/min)	73.86±5.90	84.8±7.04	86.6±10.47	0.000**
SBP (mmHg)	108.7±8.2	113.9±11.81	112.9±9.63	0.103
DBP(mmHg)	70.7±4.73	74.8±7.48	75.76±7.38	0.011*
MAP(mmHg)	82.4±6.28	87.7±8.12	88.4±7.74	0.004*

Data were expressed as mean ±SD

* Means there was a significant difference in HR between the three groups (P<0.05)

** Means there was a highly significant difference in HR between three groups (P <0.01)

Mean parameters at tenth minute:

At tenth minute, the heart rate in group B and C becomes comparable with their baseline values. Whereas in group A it is maintained at a level lessthan their baseline.

The blood pressure and mean arterial pressure in group B becomes comparable to its baseline value.

In group A it's less than that of the baseline value but in group C there is a rise in these parameters and more than that of their baseline values.

With these tables and charts, it's possible to found out that there is a significant difference exists between three groups grossly but in order to find out the significant difference that exists in between which two groups we need to do further statistical analysis like Tukey and Duncan tests. So the Tukey's test was done and the results are given below.

Preoperative comparison between three groups:

preop	HR	SBP	DBP	MAP
Between group A&B	0.001**	0.816	0.709	0.896
Between group B&C	0.130	0.000**	0.004*	0.000**
Between group C&A	0.056	0.001**	0.001**	0.001**

Data is expressed as P value

* Means there was a significant difference in HR between the three groups (P<0.05)

** Means there was a highly significant difference in HR between three groups (P <0.01)

Pre induction comparison between three groups:

Pre induction	HR	SBP	DBP	MAP
Between group A&B	0.041*	0.847	0.616	0.716
Between group B&C	0.567	0.000**	0.000**	0.000**
Between group C &A	0.138	0.000**	0.000**	0.000**

Comparison between three groups at the time of induction:

T0	HR	SBP	DBP	MAP
Between group A&B	0.145	0.007**	0.145	0.043*
Between group B&C	0.005**	0.892	0.248	0.537
Between group C&A	0.010*	0.010*	0.010*	0.009*

Comparison between three groups at the first minute of intubation:

T1	HR	SBP	DBP	MAP
Between group A&B	0.000**	0.000**	0.000**	0.000**
Between group B&C	0.000**	0.000**	0.000**	0.000**
Between group C&A	0.000**	0.000**	0.000**	0.000**

Comparison between three groups at the third minute of intubation:

T3	HR	SBP	DBP	MAP
Between group A&B	0.000**	0.006**	0.144	0.041*
Between group B&C	0.002**	0.000**	0.000**	0.000**
Between group C &A	0.000**	0.000**	0.000**	0.000**

Comparison between three groups at the fifth minute of intubation:

T5	HR	SBP	DBP	MAP
Between group A&B	0.000**	0.469	0.433	0.370
Between group B&C	0.000**	0.015*	0.000**	0.000**
Between group C &A	0.000**	0.002**	0.000**	0.000**

Comparison between three groups at the tenth minute of intubation:

T10	HR	SBP	DBP	MAP
Between group A&B	0.000**	0.045*	0.020*	0.007**
Between group B&C	0.381	0.069	0.589	0.729
Between group C&A	0.000**	0.105	0.005**	0.002**

Data is expressed as P value

* Means there was a significant difference in HR between the three groups ($P<0.05$)

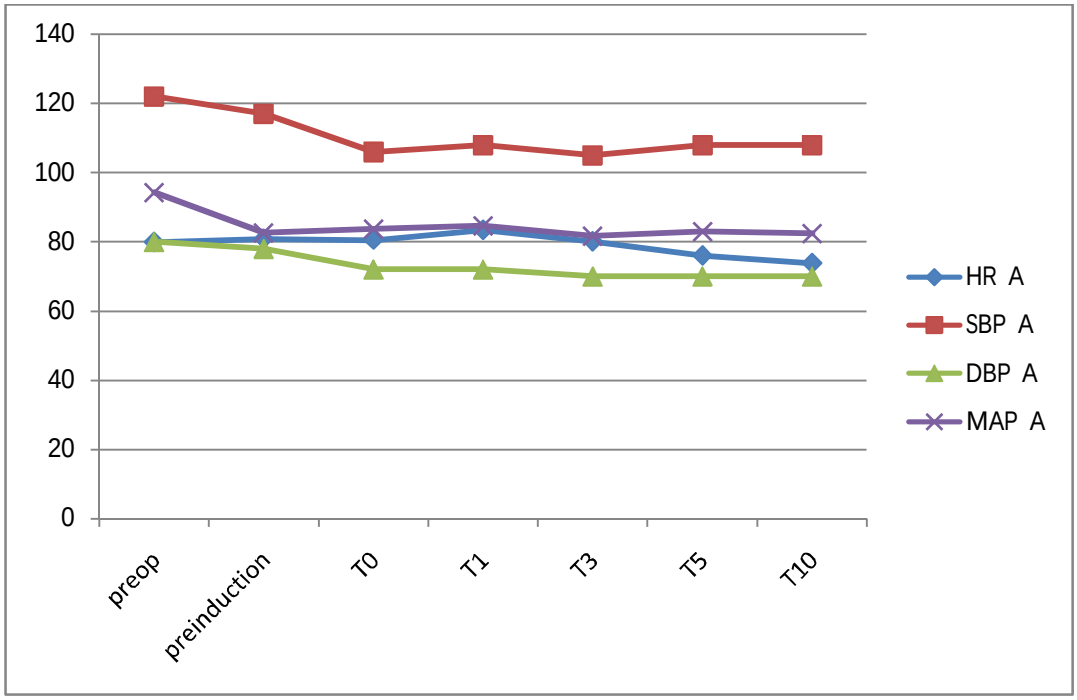
**Means there was a highly significant difference in HR between three groups ($P <0.01$)

With this Tukey analysis, in comparing group A and C there is a significant difference in HR and MAP at the time of intubation (T0) and highly significant at the first, third, fifth and tenth minute after intubation.

In between group A and B, there is a highly significant difference in the HR at all the times after intubation indicating both the drugs had different response in heart rate reduction. In case of MAP, there is a significant difference at the time of intubation, at first and third minute and no significant difference after third minute indicating that both the drugs have some similar efficacy in controlling the blood pressure.

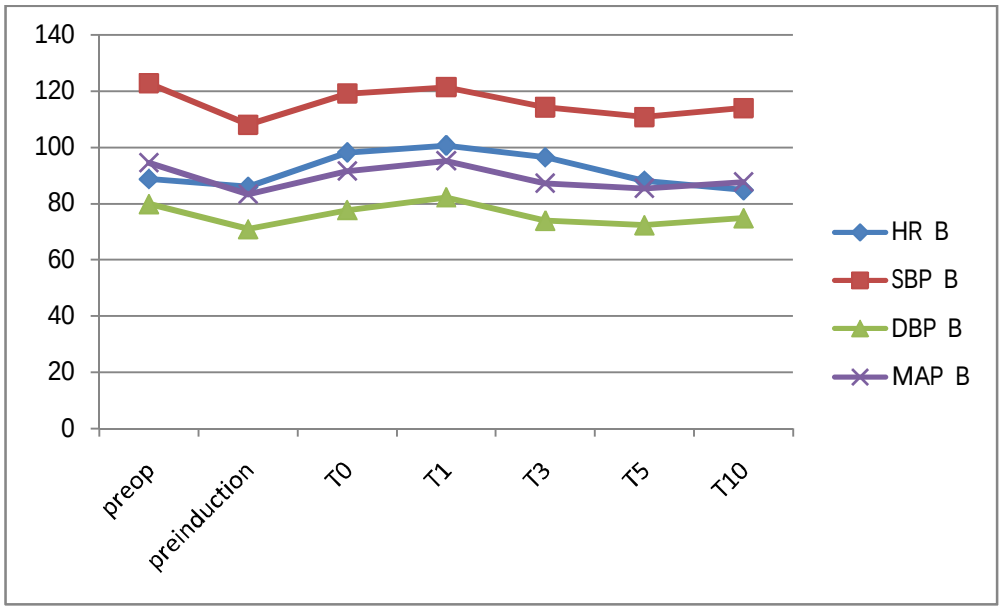
In between group B and C, there is a highly significant difference in HR and MAP at the time, first, third and fifth minute after intubation. Even at the time of preinduction, there is a significant difference in MAP which indicates the drug used in group B has more effect in controlling the blood pressure than heart rate.

Vital parameters in group A:



All parameters in group A like heart rate, systolic, diastolic pressure and mean pressures remained at or below the baseline at any time after intubation.

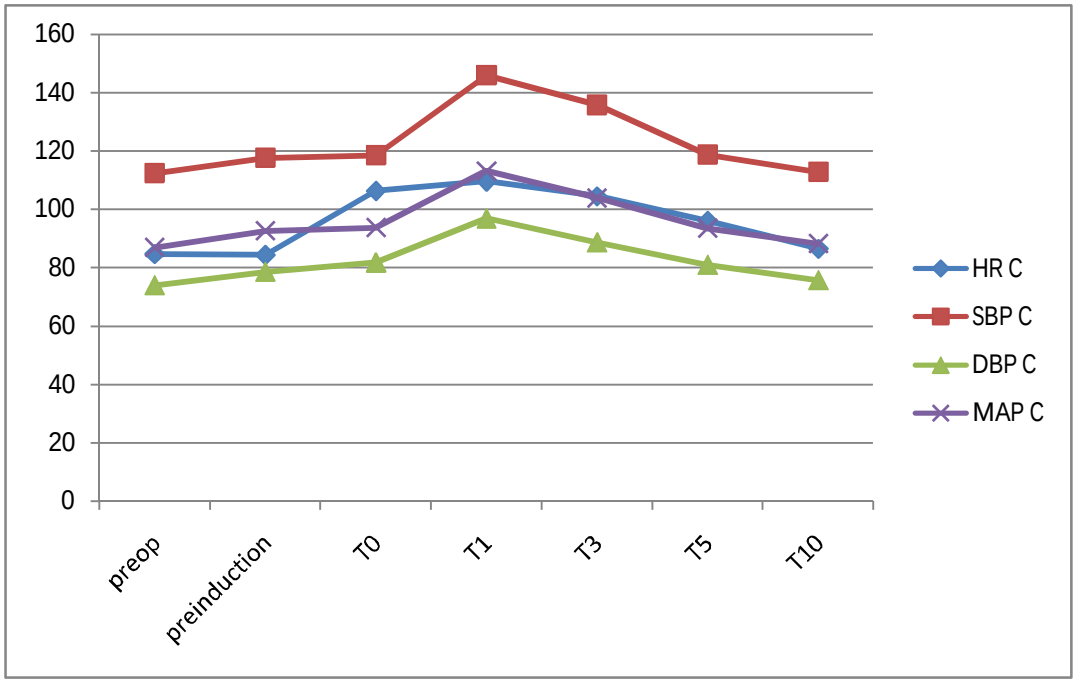
Vital parameters in group B:



In group B, the blood pressure and mean arterial pressure remained around the baseline values at and after intubation without any increase in their values.

In case of heart rate, there is a rise after intubation but that too not significant statistically. The heart rate is going in a decreasing trend steadily after 3rd minute which can be due to decreasing concentration of noradrenaline and adrenaline levels.

Vital parameters in group C:



In this group C, all the parameters heart rate, blood pressure and mean arterial pressure increases to this stimuli of laryngoscopy and intubation and are statistically significant from the baseline value.

Table for post operative sedation:

GROUP	POST OP SEDATION		TOTAL
	Yes	No	
A	0	30	30
B	20	10	30
C	0	30	30
TOTAL	20	70	90

In group B, there is sedation in around 66.7% patients and no significant sedative effect in 33.3% of patients.

DISCUSSION

Though the patients are well anaesthesized before performing laryngoscopy and tracheal intubation, reflex cardiovascular response to this noxious stimuli arises as described by Reid and Brace[9]. Orotracheal intubation with the use of laryngoscope normally needs elevation of epiglottis, thereby exposing the glottic opening. This maneuver causes sympathetic activation leading to tachycardia and hypertension. Increase in pulse pressure of around 10 mmHg is associated with 20% or evenhigher increased risk of any events occuring in our renal, cardiovascular and central nervous systems in both hypertensive and normotensive individuals.[40] Many anasthetic techniques and different drugs like opioids(fentanyl, remifentanil[44], alfentanil) beta blockers (esmolol, labetalol, metoprolol, earlier bunitrolol, propanolol), calcium channel blockers (verapamil,diltiazem, nicardipine) vasodilators (nitroglycerine, sodium nitropruside) intravenous lignocaine and newer drugs like gabapentin[45], pregabalin with various doses were tried to blunt this reflex pressor response, but none proved to attenuate fully this reflex cardiovascular action. Many drugs used in the past to reduce this response is associated with some adverse effects.

Jakobsen and coworkers used 100mg metoprolol for hysterectomy under general anaesthesia and found it to be useful in reducing the

cardiovascular stress response and catecholamine surge to laryngoscopy and intubation. Poupak rahimzadeh and coworkers used metoprolol specifically in nasal surgeries and found it to be effective not only in blunting the laryngoscopic and intubation response but also less bleeding and clear field for the surgeon to operate due to hypotension caused by metoprolol. They concluded that repetitive doses or large doses are needed to do such effect. So we decided to evaluate to effects of metoprolol further and took as one of our study drug.

Gabapentin and Pregabalin are structural analogues of gamma amino butyric acid, initially developed for the treatment of epilepsy and also for the effective management of neuropathic pain. They are also used in the perioperative period in order to provide pain relief.

Recently these drugs are being used in the preoperative setting to blunt the cardiovascular stress response occuring to laryngoscopy and tracheal intubation but with different doses and conflicting results[37,40, 46].

Howard N.Bockrader and coworkers did a comparison of the pharmacokinetics and pharmacodynamics of gabapantin and pregabalin. Gabapentin takes atleast three hours to attain peak concentration in the plasma whereas pergabalin reaches its highest concentration around an hour. Gabapentin follows zore order kinetics and is unpredictable and non linear. The absorption of pregabalin folloes first order kinetics with

bioavailability >90%. So in summary, pharmacokinetics of pregabalin is distinct with better pharmacodynamics.In another study, Snehaaltha Bashyam and collegues did a comparison between 600mg of gabapentin with 150 mg of pregabalin for anxiolysis, sedation and blunting the stress response. The medications were given one hour prior to the surgery. In conclusion, it has been found pregabalin to be better than gabapentin in maintaining the hemodynamics, sedation and anxiolysis without significant adverse effects. Namratha and coworkers did a evaluation of gabapentin and pregabalin for blunting the pressor response with 800mg and 150 mg respectively. It has been found that pregabalin is better than gabapentin in attenuating this cardiovascular sress response.

So we took pregabalin as another drug and evaluated its effect in blunting the response to laryngoscopy and intubation.

In our study,we evaluated the effectiveness of oral metoprolol and pregabalin given one hour before surgery in blunting the reflex pressor effect occuring with laryngoscopy and intubation .Ninety patients were enrolled in the study with thirty patients in each group and named as group A, group B and group C. Patients in group A received 100mg metoprolol, group B were given 150mg pregabalin and group C got the placebo.

In our study, there was a significant rise in heart rate and blood pressure following laryngoscopy and intubation in the group C. This is consistent with the study done by Matthew D. Mullet and coworkers. In their study, they established that oropharyngeal stimulation will rise the heart rate and blood pressure whether the individual is conscious, sedated or anaesthesized.so then they used local anaesthetics to spray on the upper airway to blunt the neurovascular stress response and found it to be one of the effective means to reduce the occurrence of complications. In another similar study like this, in that Manjunath and colleagues used 10% lignocaine spray to the posterior pharynx before indution of anesthesia and found some significant decrease in the stress response.

Fauzia khan and coworkers did a meta analysis taking 72 RCT's and found that pharmacological agents like instillation of local anasthetics, beta blockers, calcium channel blockers or opioids are necessary to reduce the risk of arrhythmias and other adverse effects associated with laryngoscopy and tracheal intubation.

In our study, we found there is no rise in heart rate and blood pressure with single dose of 100mg metoprolol (in group A) for the expected hypertensive and tachycardic response to laryngoscopy and intubation and the HR amd MAP are all below the baseline values. This is consistent with the study done by Saarnivaara and colleagues, they found

that not only the stimulation of glossopharyngeal and vagus nerves causes this reflex response of tachycardia, hypertension and cardiac arrhythmias,use of drugs to facilitate induction and intubation like thiopentone and succinyl choline also causes QT prolongation thereby cardiac arrhythmias. In conclusion of this study, the drugs practolol and metoprolol were found to be effective in preventing QT prolongation and dysarrhythmias.

Similar to our study, Derbyshine and coworkers found in their study there was a significant correlation betweentracheal intubation and plasma catecholamine levels i.e there is a increase in adrenaline and noradrenaline level in the plasma following induction and subsequent intubation. Pristautz and colleagues in their study used β adrenolytic premedication and found it to be useful in patients to obtund the reflex stress response.

In our study in group B,with single dose of 150mg pregabalin, the rise in heart rate and mean arterial pressure are not significant and reached the baseline within ten minutes of intubation.

This result is consistent with the study done by Talikoti and coworkers, who compared preservative free intravenous lignocaine of 1.5mg/kg with 150mg pregabalin. Pregabalin was given 3 hours before surgery and I.V. lignocaine given 3 minutes before intubation. This study

concluded that Lignocaine is better than pregabalin in blunting the increase in heart rate and pregabalin is better for reduction in diastolic pressure and mean arterial pressure.

Eren and colleagues used pregabalin to know its effectiveness in blunting the hemodynamic response to intubation in lumbar surgeries and found to be effective in preventing this stress response.Further more its use is associated with preoperative anxiolysis, prevention of chronic pain,nausea and vomiting postoperatively and decrease the incidence of delirium. Similarly in our study also, pregabalin is effective in decreasing the stress response.

Similarly,Rastogi bhawan and coleagues used two various doses of pregabalin inorder to find out the clinically effective and safe dose during airway manipulation to maintain the hemodynamics. The study was done with 75mg and 150mg doses given one hour before the procedure. The response is found to be dose dependent and 150 mg pregabalin reduced the stress response significantly and maintained stable hemodynamics intraoperatively without any prolongation in the recovery time.

Thus it indicates that both the drugs succeeded in blunting the pressor response to laryngoscopy and intubation when compared with the control group where there is highly significant rise in HR, blood pressure

and MAP and are well above the baseline parameters till tenth minute after intubation.

In agreement with the study by Tilakoti and coworkers, the reduction in blood pressure and mean arterial pressure is more than the reduction in heart rate in group B (pregabalin 150mg) in this study also.

The mechanism by how pregabalin blunts the cardiovascular effects to laryngoscopy and intubation is not clear till now but it has been postulated to be due to its action against nociceptive mechanism. This mechanism most likely modifiesthe calcium current selectively by binding to the voltage gated Ca^{2+} channels and act in the same way as calcium channel blockers in maintaining the cardiovascular hemodynamics.

As beta blockers are known to reduce heart rate and blood pressure even in the intraoperative period also, there is no occurrence of bradycardia or hypotension which necessiates treatment. Pregabalin is known to have sedative effect[46], there is no significant drowsiness in patients who were given pregabalin. This is consistent with the study done by Kumkum Gupta and colleagues.

Though we had results consisent with many other studies done earlier, but we have certain limitations. We took only 30 patients in each

group, this sample size is small. Another limitation is we took patients belonging to ASA I and ASA II, so this we cannot extend the result of this study to use in ASA III and ASA IV patients who are the persons more sensitive to noxiuos stimuli of laryngoscopy and intubation and more prone to complications than normal individuals.

SUMMARY

In this study

1. We observed both metoprolol and pregabalin group had significant response of blunting the tachycardic and hypertensive response to laryngoscopy and intubation than the control group.
2. In pregabalin group, there is a slight raise in pulse rate and blood pressure but not significant statistically. Only in heart rate, there is a increase above the patient's baseline but settles around fifth minute after intubation itself.
3. Intra operative bradycardia and hypotension in both the groups (metoprolol and pregabalin) were comparable.

CONCLUSION

With this study, both metoprolol and pregabalin are found to be good in attenuating the cardiovascular response to laryngoscopy and intubation when compared with the control group. The blunting of heart rate response is less with pregabalin than with metoprolol. Hence we conclude, metoprolol is found to be better than pregabalin in blunting the cardiovascular stress to laryngoscopy and intubation.

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INSTITUTIONAL ETHICAL COMMITTEE
GOVT. KILPAUK MEDICAL COLLEGE,
CHENNAI-10

Protocol ID. No.03/03/2015 Meeting held on 26/03/2015

CERTIFICATE OF APPROVAL

The Institutional Ethical Committee of Govt. Kilpauk Medical College, Chennai reviewed and discussed the application for approval "Randomized controlled study comparing oral metoprolol and oral pregabalin for attenuation of cardiovascular responses to laryngoscopy and tracheal intubation – For Dissertation Purpose" submitted by Dr.K.Nandhini, MD (Anaesthesia), Post Graduate Student, Govt. Kilpauk Medical College, Chennai.

The Proposal is APPROVED.

The Institutional Ethical Committee expects to be informed about the progress of the study any Adverse Drug Reaction Occurring in the Course of the study any change in the protocol and patient information /informed consent and asks to be provided a copy of the final report.

CHAIRMAN, 15/4/15
Ethical Committee
Govt. Kilpauk Medical College, Chennai

PROFORMA

Name: Age/sex: IP no:

Wt in kg: Ht in cm:

Pre Op:

History:

Examination: CVS: RS:

Airway: MPC I II III IV

Investigations: Hb: RBS: Urea: Creat:

ECG: ECHO:

ASA: PS I PS II PS III PS IV

Study group:

Duration of surgery:

TIME	HR	SBP	DBP	MAP
Pre op				
Preinduction				
T0				
T1				
T3				
T5				
T10				

Intraop Hypotension: Yes No

IntraopBradycardia: Yes No

Postop sedation: Yes No

PATIENT CONSENT FORM

Study title: RANDOMISED CONTROLLED STUDY COMPARING ORAL METOPROLOL AND ORAL PREGABALIN FOR ATTENUATION OF CARDIOVASCULAR RESPONSES TO LARYNGOSCOPY AND TRACHEAL INTUBATION

Study centre: Department of Anaesthesiology,

Government Kilpauk Medical college,

Chennai-10.

Participant name: Age: Sex: I.P. No:

I confirm that I have understood the purpose of the procedure for the above study. I have the opportunity to ask the question and all my questions and doubts have been answered to my satisfaction.

I have been explained about the pitfall of the procedure. I have been explained about the safety, advantage and disadvantage of the technique.

I understand that my participation in the study is voluntary and that I am free to withdraw at anytime without giving any reason.

I understand that investigator, regulatory authorities and the ethical committee will not need my permission to look at my health records both in respect to the current study and any further research that may be conducted in relation to it, ven if I withdraw from the study. I understand that my identity will not be revealed in any information released to the third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from the study.

Time: Signature/thumb impression of the pt:

Date: Name of the Participant:

Place:

Signature of the investigator:

Name of the investigator:

நோயாளி ஒப்புதல் படிவம்

ஆராய்ச்சியின் விவரம் :

ஆராய்ச்சி மையம் : அரசு கீழ்பாக்கம் மருத்துவக் கல்லூரி மருத்துவமனை

நோயாளியின் பெயர் : நோயாளியின் வயது:

பதிவு எண் :

நோயாளி கீழ்கண்டவற்றுள் கட்டங்களை (✓) செய்யவும்

1 மேற்குறிப்பிட்டுள்ள ஆராய்ச்சியின் நோக்கத்தையும் பயனையும் முழுவதுமாக புரிந்து கொண்டேன். மேலும் எனது அனைத்து சந்தேங்களையும் கேட்டு அதற்கான விளக்கங்களையும் தெளிவுபடுத்திக் கொண்டேன். ☐

2 மேலும் இந்த ஆராய்ச்சிக்கு எனது சொந்த விருப்பத்தின் பேரில் பங்கேற்கிநேன் என்றும், மேலும் எந்த நேரத்திலும் எவ்வித முன்றிவிப்பு மின்றி இந்த ஆராய்ச்சியிலிருந்து விலக முழுமையான உரிமை உள்ளதையும் இதற்கு எவ்வித சட்ட பிணைப்பும் இல்லை என்பதையும் அறிவேன். ☐

3 ஆராய்சியாளரோ, ஆராய்ச்சி உதவியாளரோ, ஆராய்ச்சி உபயத்தாரரோ, ஆராய்ச்சி பேராசிரியரோ, ஒழுங்குநெறி செயற்குழு உறுப்பினர்களோ எப்போது வேண்டுமானாலும் எனது அனுமதியின்றி எனது உள்நோயாளி மற்றும் புற நோயாளி பதிவுகளை இந்த ஆராய்ச்சிக்காகவோ அல்லது எதிர்கால பிறஆராய்ச்சிகளுக்காகவோ பயன்படுத்திக் கொள்ளலாம் என்றும் மேலும் இந்த நிபந்தனை நான் இவ்வராய்ச்சிலிருந்து தகும் என்றும் ஒப்புக்கொள்கிறேன். ஆயினும் எனது அடையாளம் சம்பந்தப்பட்ட எந்த பதிவகளும் (சட்டபூர்வமான தேவைகள் தவிர) வெளியிடப்படமாட்டது என்ற உறுதிமொழியின் பெயரில் இந்த ஆராய்ச்சிலிருந்து கிடைக்கப்பெறும் முடிவுகளை வெளியிட மறுப்பு தெறிவிக்கமாட்டேன் என்று உறுதியளிக்கிறேன். ☐

4. இந்த ஆராய்ச்சிஆச்ன வாயின் அருகில் வரும் சீழ் கட்டியை குறித்தது. அந்த நோயின் தன்மையையும், பின் விளைவுகளையும் பற்றியும், அறுவை சிகிச்சையின் போது கீறி எடுக்கப்படும் சீழை பரிசோதனைக்கு அனுப்பி கிருமியின் தன்மையையும் அதற்கு உகந்த மருந்தை பற்றியும் அறிய நடத்தும் ஆராய்ச்சி என்பதை மருத்துவர் மூலம் அறிந்து கொண்டேன். ☐
5. இந்த ஆராய்ச்சிக்கு நான் முழுமனதுடன் சம்மதிக்கின்றேன் என்றும் மேலும் ஆராய்ச்சி குழுவினர் எனக்கு அளிக்கும் அறிவுரைகளை தவறாது பின்பற்றுவேன் என்றும் உறுதியளிக்கிறேன். ☐
6. இந்த ஆராய்ச்சிக்குத் தேவைப்படும் அனைத்து மருத்துவப்பரிசோதனைகளுக்கும் ஒத்துழைப்பு தருவேன் என்று உறுதியளிக்கிறேன். ☐
7. இந்த ஆராய்ச்சிக்கு யாருடைய எற்புறுத்தலுமின்றி எனது சொந்த விருப்பத்தின் பேரிலும் சுயஅறிவுடனும் முழுமனதுடனும் சம்மதிக்கின்றேன் என்று இதன் மூலம் ஒப்புக்கொள்கிறேன். ☐

நோயாளியின் கையொப்பம் / பெருவிரல் கைரேகை
இடம்: தேதி:

ஆராய்ச்சியாளரின் கையொப்பம்:
இடம்: தேதி:

MASTER CHART

name	age	gender	MPC	group	pre op HR	pre op SBP	pre op DBP	pre op MAP	HR PI	SBP PI	DBP PI	MAP PI	HR T0	SBP T0	DBP T0	MAP T0	HR T1	SBP T1	DBP T1	MAP T1	HR T3	SBP T3	DBP T3	MAP T3	HR T5	SBP T5	DBP T5	MAP T5	HR T10	SBP T10	DBP T10	MAP T10	IOB	IOH	POS
mary	27	F	II	A	80	127	85	99	78	118	64	82	80	101	74	83	83	99	70	80	79	88	58	68	72	86	58	67	72	101	66	72	N	N	N
hemalata	25	F	II	A	85	121	86	97	93	93	52	62	89	93	59	70	87	93	59	70	87	96	69	78	90	110	75	87	86	103	72	82	N	N	N
usha	32	F	I	A	88	128	82	96	88	97	66	76	103	125	98	107	105	122	79	93	90	98	71	80	72	102	74	83	75	108	75	86	N	N	N
sajitha	34	F	II	A	80	127	85	99	78	118	85	96%	80	101	74	83	83	99	70	80	79	88	58	68	72	86	58	67	72	101	66	72	N	N	N
kutti mani	28	M	II	A	75	128	81	96	85	97	66	76	82	108	70	83	83	118	82	94	80	117	80	92	78	120	72	88	75	110	70	83	N	N	N
natarajan	40	M	II	A	75	118	70	86	77	103	61	74	80	90	55	67	76	93	60	71	71	91	58	69	69	99	60	73	64	98	59	72	N	N	N
anand babu	22	M	II	A	78	120	72	88	73	109	73	85	84	122	78	93	75	113	73	86	76	110	68	82	72	106	66	79	72	100	64	76	N	N	N
perumal	42	M	II	A	78	114	72	86	77	101	68	79	75	108	70	83	79	118	77	91	75	112	70	84	70	108	68	81	71	108	68	81	N	N	N
lakshmi	42	F	II	A	85	129	85	100	84	100	60	73	82	124	80	95	86	131	87	102	81	128	83	98	79	124	80	95	75	122	74	90	N	N	N
shakthi	29	F	I	A	80	130	80	97	79	119	83	95	76	127	76	93	85	134	84	101	79	130	80	97	74	126	72	90	76	124	70	88	N	N	N
roy	40	M	II	A	78	119	82	94	75	101	68	79	70	116	78	91	79	120	80	93	74	119	78	92	71	119	76	90	72	116	74	88	N	N	N
geetha	24	F	I	A	80	121	82	95	82	118	85	96	80	100	80	83	79	106	82	90	83	110	81	90	78	118	74	89	72	116	72	83	N	N	N
ramesh	30	M	I	A	71	120	85	97	69	123	78	93	65	114	80	91	72	120	83	95	69	117	82	94	66	114	79	91	65	110	74	86	N	N	N
ramasamy	44	M	I	A	75	124	81	95	73	101	68	79	71	120	75	90	80	129	80	96	79	125	78	93	75	126	76	92	70	122	74	90	N	N	N
murugan	36	M	I	A	82	118	76	90	80	103	70	81	79	104	72	82	87	106	70	82	83	115	70	85	79	120	75	90	72	118	73	88	N	N	N
shankaran	28	M	II	A	76	126	83	97	75	100	60	73	73	121	76	91	82	115	70	85	81	105	68	80	77	108	71	83	72	112	75	87	N	N	N
meena	22	F	I	A	85	121	86	97	93	109	73	85	89	93	59	70	87	93	59	70	88	96	69	78	90	110	75	87	83	103	72	82	N	N	N
nandhini	24	F	II	A	80	127	85	99	78	103	61	74	80	101	74	83	83	99	70	80	79	88	58	68	72	86	58	67	72	101	66	72	N	N	N
gowri	35	F	II	A	88	118	75	89	88	118	64	82	86	91	63	72	90	93	62	72	88	90	60	70	87	102	66	78	88	112	78	89	N	N	N
nagarajan	44	M	II	A	75	118	70	86	77	97	66	76	80	90	55	67	76	93	60	71	71	91	58	69	69	99	60	73	64	98	59	72	N	N	N
ayyanar	33	M	I	A	75	128	81	96	85	119	83	95	82	108	70	83	83	118	82	94	80	117	80	92	78	120	72	88	75	110	70	83	N	N	N
mangai	18	F	I	A	88	115	90	98	90	123	78	93	86	90	70	77	90	91	68	78	88	95	70	78	86	95	72	80	82	92	75	80	N	N	N
kanga	32	F	I	A	88	128	82	96	88	101	68	79	93	125	98	107	97	122	79	93	90	98	71	80	72	102	74	83	75	108	75	86	N	N	N
ramasamy	42	M	II	A	78	119	82	94	75	124	70	88	70	100	75	83	79	102	80	87	74	110	80	90	71	119	76	90	72	116	74	88	N	N	N
moorthy	36	M	I	A	82	118	76	90	80	103	70	81	79	104	72	82	87	106	70	82	83	115	70	85	79	120	75	90	72	118	73	88	N	N	N
rani	35	F	II	A	80	127	85	99	78	101	68	79	80	101	74	83	83	99	70	80	79	88	58	68	72	86	58	67	72	101	66	72	N	N	N
rasu	44	M	I	A	76	126	83	97	75	123	78	93	73	121	76	91	82	115	70	85	81	105	68	80	77	108	71	83	72	112	75	87	N	N	N
rajini	21	M	II	A	80	118	80	93	75	97	66	76	70	116	78	91	79	120	80	93	74	119	78	92	71	119	76	90	72	116	74	88	N	N	N
rajeswari	23	F	I	A	85	121	86	97	93	118	85	96	89	93	59	70	87	93	59	70	87	96	69	78	90	110	75	87	86	105	72	83	N	N	N
remila john	28	F	I	A	72	110	70	83	88	118	64	82	90	98	54	68	78	98	60	76	75	99	62	74	73	102	70	80	70	100	68	78	N	N	N
usha	27	F	I	B	96	110	68	82	89	110	72	85	109	139	94	109	112	126	74	91	108	110	57	75	85	106	59	75	83	114	67	83	N	N	Y
jayasudha	30	F	II	B	85	114	72	86	85	108	70	82	85	105	69	81	96	106	77	86	93	106	76	86	85	103	76	85	85	102	75	84	N	N	Y
ravi	45	M	II	B	76	105	84	91	72	103	80	88	95	115	85	95	98	101	70	80	95	97	68	78	90	92	65	74	85	92	67	75	N	N	N
deva	19	M	II	B	86	124	71	89	79	119	68	85	104	90	51	64	114	128	81	97	120	130	80	96	101	128	73	91	89	126	74	91	N	N	N
chellaiya	45	M	II	B	93	131	82	98	100	108	72	84	108	129	76	94	93	122	77	92	95	122	76	91	86	119	80	93	90	124	83	96	N	N	Y
shanthi	55	F	I	B	95	142	91	108	92	105	68	80	100	125	75	92	101	128	91	103	98	125	84	98	94	118	79	92	90	125	85	98	N	N	Y
heena	18	F	II	B	102	143	90	109	100	117	72	87	110	98	59	72	120	149	100	117	110	131	76	94	99	121	74	90	95	120	73	89	N	N	Y
thenmozhi	34	F	II	B	110	144	99	121	111	98	72	81	110	123	79	94	106	122	79	93	99	118	77	91	98	118	79	92	95	124	80	94	N	N	Y
dhanapal	35	M	II	B	87	110	83	92	96	97	73	81	101	103	72	82	97	102	72	82	92	99	71	84	98	99	66	78	83	103	74	83	N	N	N
farhana	37	F	II	B	65	113	60	78	68	92	53	66	87	146	95	112	84	114	77	89	80	101	63	76	67	101	66	78	69	123	80	94	N	N	N
varalakshmi	19	F	I	B	84	130	87	101	72	109	63	78	78	97	57	70	94	127	93	104	76	108	71	83	83	111	75	87	75	106	62	77	N	N	Y
raghu	24	M	I	B	86	124	71	89	79	119	68	85	104	90	51	64	114	128	81	97	120	130	80	96	101	128	73	91	89	126	74	91	N	N	Y
chellamuthu	42	M	I	B	76	105	84	91	72	103	80	88	95	115	85	95	98	111	94	100	95	105	85	78	80	92	65	74	85	92	67	75	N	N	Y
raji	32	M	I	B	96	110	68	82	89	110	72	85	109	139	94	109	112	126	74	91	108	110	57	75	85	106	59	75	83	114	67	83	N	N	Y
vinayagam	36	M	I	B	87	110	83	92	96	97	73	81	101	103	72	82	97	102	72	82	92	99	71	84	98	99	66	78	83	103	74	83	N	N	N
narayani	40	F	II	B	96	110	68	82	89	110	72	85	109	139	94	109	112	126	74	91	108	110	57	75	85	106	59	75	83	114	67	83	N	N	Y
prabakaran	38	M	I	B	84	130	87	101	72	109	63	78	78	97	57	70	94	127	93	104	76	108	71	83	83	111	75	87	75	106	62	77	N	N	Y
mahalakshmi	37	F	II	B	65	113	60	78	68	92	53	66	87	146	95	112	84	114	77	89	80	101	63	76	67	101	66	78	69	123	80	94	N	N	Y
sahana bee	30	F	II	B	85	114	72	86	85	108	70	82	85	105	69	81	96	106	77	86	93	106	76	86	85	103	76	85	85	102	75	84	N	N	N
kalaimani	42	M	II	B	76	105	84	91	72	103	80	88	95	115	85	95	85	101	70	80	84	97	68	78	80	92	65	74	85	92	67	75	N	N	Y
leela	19	F	I	B	93	131	82	98	100	108	72	84	108	129	76	94	93	122	77	92	95	122	76	91	86	119	80	93	90	124	83	96	N	N	N
samykarinu	33	M	I	B	108	142	91	108	96	105	68	80	100	125	75	92	101	128	91	103	92	125	84	98	90	118	79	92	94	125	85	98	N	N	Y
marusamy	39	M	I	B	96	110	68	82	89	110	72	85	109	139	94	109	112	126	74	91	108	110	57	75	85	106	59	75	83	114	67	83	N	N	N
rajathi	31	F	II	B	76	105	84	91	72	103	80	88	95	115	85	95	98	101	70	80	95	97	68	78	90	92	65	74	85	92	67	75	N	N	N
chandru	20	M	I	B	95	142	91	108	92	105	68	80	100	125	75	92	101	128	91	103	98	125	84	98	94	118	79	92	90	125	85	98	N	N	Y
akilan	25	M	I	B	102	143	90	109	100	117	72	87	110	98	59	72	120	149	100	117	110	131	76	94	99	121	74	90	95	120	73	89	N	N	Y
chitra	29	F	II	B	86	127	78	94	83	124	78	93	92	133	92	105	90	130	90	103	89	126	87	100	85	125	87	100	80	121	82	95	N	N	N
mukunthan	34	M	II	B	84	128	79	95	82	125	79	94	91	134	93	106	89	131	91	104	88	127	87	100	84	126	87	100	79	122	83	96	N	N	Y
vetriselvi	24	F	I	B	108	142	91	108	96	105	68	80	100	125	75	92	101	128	91	103	92	125	84	98	90	118	79	92	94	125	85	98	N	N	Y
malliga	27	F	I	B	83	126	78	94	81	123	78	93	90	132	92	105	108	130	90	103	105	125	87	100	92	124	86	99	78	120	82	95	N	N	Y
akila	31	F	II	C	82	111	82	92	85	107	73	84	94	88	61	70	100	136	91	106	85	134	73	94	78	105	72	83	76	106	72	83	N	N	N
prakash	20	M	I	C	73	114	76	85	74	114	74	94	78	88	50	63	95	121	83	96	98	122	74	90	103	125	90	102	85	110	80	90	N	N	N
vijaykumar	41	M	II	C	74	110	79	89	78	127	90	109	125	124	81	95	103	154	80	105	101	116	78	91	94	107	72	84	88	105	70	82	N	N	N
rajarajan	28	M	II	C	94	108	67	82	94	107	73	84	128	127	79	95	120	170	109	129	108	140	88	105	110	120	77	91	100	115	72	89	N	N	N

MASTER CHART

rajamani	35	F	I	C	74	110	79	89	78	125	88	103	125	124	81	95	103	120	80	93	101	116	78	91	94	107	72	84	88	105	70	82	N	N	N
nagabushnam	35	M	II	C	89	127	79	95	82	115	75	88	112	148	99	115	113	150	100	117	108	135	79	94	102	117	84	95	101	115	85	95	N	N	N
sarathkumar	23	M	I	C	69	130	83	99	68	116	70	85	101	163	115	131	93	157	107	124	90	144	87	106	90	132	90	104	73	118	77	91	N	N	N
sasikala	25	F	II	C	102	103	68	80	100	112	70	84	108	103	68	80	126	150	110	123	117	154	111	125	102	146	110	122	95	128	85	99	N	N	N
rosy	19	F	I	C	78	97	62	74	82	128	84	99	95	125	90	102	100	150	90	110	112	140	92	107	90	96	58	71	83	93	60	71	N	N	N
murugammal	35	F	II	C	67	106	71	83	79	130	79	96	88	98	67	77	99	150	103	119	90	147	97	114	89	131	81	97	70	124	80	94	N	N	N
palani	38	M	I	C	102	103	68	80	100	118	80	93	108	103	68	80	126	150	110	123	132	154	111	125	116	146	110	122	107	128	85	99	N	N	N
chennimalai	30	M	II	C	94	108	67	82	94	119	80	93	128	127	79	95	120	170	109	129	108	140	88	105	110	120	77	91	100	115	72	89	N	N	N
sarasu	37	F	I	C	83	126	78	94	81	118	84	95	90	100	80	83	110	130	90	103	108	125	87	100	90	124	86	99	78	120	82	95	N	N	N
vimala	40	F	I	C	102	103	68	80	100	124	79	94	108	146	110	122	126	150	110	123	132	154	111	125	116	103	68	80	107	128	85	99	N	N	N
kavin	29	M	I	C	98	105	75	85	88	116	75	87	105	121	100	107	120	145	98	113	108	135	95	108	98	115	80	91	82	106	70	82	N	N	N
naveena	21	F	II	C	78	97	62	74	82	125	80	95	95	125	90	102	100	150	90	110	112	140	92	107	90	96	58	71	83	93	60	71	N	N	N
kathir	25	M	II	C	69	130	83	99	68	114	74	94	101	163	115	131	93	157	107	124	90	144	87	106	90	132	90	104	73	118	77	91	N	N	N
kirubakaran	26	M	I	C	89	127	79	95	82	107	73	84	112	148	99	115	113	150	100	117	108	135	79	94	102	117	84	95	101	115	85	95	N	N	N
saranya	24	F	I	C	82	111	82	92	85	108	75	86	94	88	61	70	100	136	91	106	85	134	73	94	78	105	72	83	76	106	72	83	N	N	N
hemalatha	27	F	II	C	74	110	79	89	78	115	75	88	125	124	81	95	103	154	80	105	101	116	78	91	94	107	72	84	88	105	70	82	N	N	N
mohan	39	M	I	C	67	106	71	83	79	125	88	103	88	98	67	77	99	150	103	119	90	147	97	114	89	131	85	100	70	124	80	94	N	N	N
chitra	22	F	II	C	83	126	78	94	81	110	90	96	90	100	80	83	110	130	90	103	108	125	87	100	90	124	86	99	78	120	82	95	N	N	N
nagaratinam	35	F	II	C	102	103	68	80	100	127	90	109	108	103	68	80	126	150	110	123	117	154	111	125	102	146	110	122	95	128	85	99	N	N	N
durai	21	M	I	C	95	134	70	91	87	118	80	93	125	124	81	95	103	120	80	93	101	116	78	91	94	107	72	84	88	105	70	82	N	N	N
venkatesan	28	M	II	C	98	105	75	85	88	116	75	87	105	121	100	107	120	145	98	113	108	135	95	108	98	115	80	91	82	106	70	82	N	N	N
anitha	19	F	I	C	94	108	67	82	85	107	73	84	100	98	67	77	115	150	103	119	97	147	97	114	90	131	81	97	85	111	80	90	N	N	N
raghavan	28	M	I	C	83	126	78	94	81	125	80	95	95	125	90	102	113	150	100	117	108	135	79	94	95	117	84	95	84	115	85	95	N	N	N
kanniappan	45	M	II	C	74	110	79	89	78	119	82	94	125	124	81	95	103	120	80	93	101	116	78	91	94	107	72	84	88	105	70	82	N	N	N
malathi	28	F	I	C	94	108	67	82	94	114	74	94	128	127	79	95	120	170	109	129	108	140	88	105	100	120	77	91	92	115	72	89	N	N	N
latha	23	F	I	C	82	111	82	92	85	123	75	91	108	103	68	80	120	145	98	113	108	135	95	108	98	115	80	91	82	106	70	82	N	N	N